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Development of silicon-containing bis-phenol derivatives as androgen receptor antagonists: Selectivity switching by C/Si exchange

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ABSTRACT

We previously reported that bis-phenol derivatives, including LG190178 (**3a**), possess not only vitamin D receptor (VDR) agonistic activity, but also androgen receptor (AR) antagonistic activity. Here, we describe the design, synthesis and evaluation of silicon-containing bis-phenol derivatives, with the objective of obtaining increased selectivity toward VDR or AR. We found that replacement of the quaternary carbon in the bis-phenol skeleton with silicon increased AR-antagonistic activity and reduced VDR-agonistic activity, that is, the AR selectivity of the silicon-containing compounds was higher than that of corresponding carbon compounds. To our knowledge, this is the first report of nuclear receptor (NR) selectivity switching by sila-substitution (C/Si exchange). Among the compounds synthesized, AR-selective ligand (***S,R***)**-3b** exhibited more potent anti-androgenic activity (IC_{50} = 0.072 μM) than hydroxyflutamide, a well-known androgen antagonist (IC_{50} = 1.4 μM), in SC-3 cell proliferation assay. These results suggest that sila-substitution is a useful approach for structural development of selective AR ligands.

1. Introduction

The biologically active form of vitamin D_3, 1α,25-dihydroxyvitamin D_3 (1,25-VD_3) (**1**) (Fig. 1), is a secosteroid hormone that regulates calcium homeostasis, bone metabolism, proliferation and differentiation of various types of cells, and is also involved in immune modulation.[1–5] Almost all of these activities of 1,25-VD_3 are considered to be mediated by binding to and activating nuclear vitamin D receptor (VDR) as a specific transcription factor.[3,4] Recently, it has been reported that 1,25-VD_3 has a potent differentiation-inducing activity in leukemic cells[6,7] and growth-inhibitory activity towards various types of cancer cells, including those of prostate, breast and colon.[8–11] Thousands of vitamin D analogs with a secosteroidal skeleton have been designed and synthesized so far.[12] 1,25-VD_3 (**1**) and other synthetic vitamin D analogs, such as alfacalcidol (**2**) (Fig. 1), have been used clinically to regulate calcium metabolism and for treatment of psoriasis and osteoporosis.[13] However, these drugs often induce side effects, such as hypercalcemia.

Boehm et al. have reported a series of nonsecosteroidal vitamin D derivatives, including LG190178 (**3a**), LG190176 (**4b**) and LG190155 (**5c**), with a bis-phenol skeleton (Fig. 2).[14,15] These compounds exhibit significant potency and activity in VDR reporter gene assays (EC_{50} = 40–600 nM), and show monocytic cell differentiation-inducing activity toward human leukemia cell line HL-60 (EC_{50} = 30–800 nM), growth inhibition of human prostate tumor cell line LNCaP (EC_{50} = 20–300 nM), regulation of VDR target gene expression in vivo, and other activities.

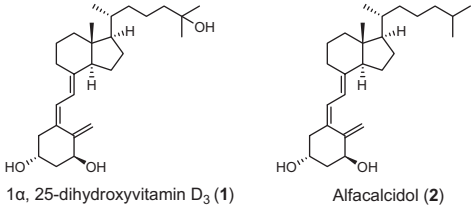

Figure 1. Chemical structures of 1α,25-dihydroxyvitamin D_3 (1,25-VD_3) (**1**) and alfacalcidol (**2**).

Recently, we reported the design and synthesis of various LG190178 analogs.[16,17] Among them, nitrogen analogs of LG190178, including (*R,S*)-DPP-1023 (**6**) (Fig. 3), showed higher vitamin D_3-agonistic activity than LG190178 (**3a**). During our structural development studies, we found that these nonsecosteroidal vitamin D derivatives also possess androgen receptor (AR) antagonistic activity.

It is clearly of interest to separate the activities of these compounds. Furthermore, sila-substitution (C/Si exchange) of existing

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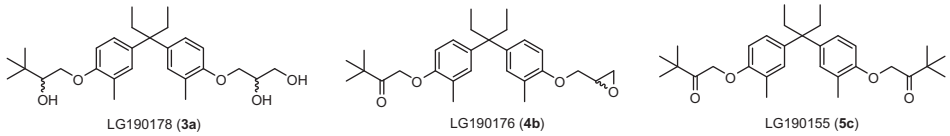


Figure 2. Chemical structures of nonsecosteroidal vitamin D derivatives, LG190178 (**3a**), LG190176 (**4a**) and LG190155 (**5a**).

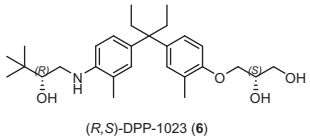


Figure 3. Chemical structure of (***R,S***)-DPP-1023 (**6**).

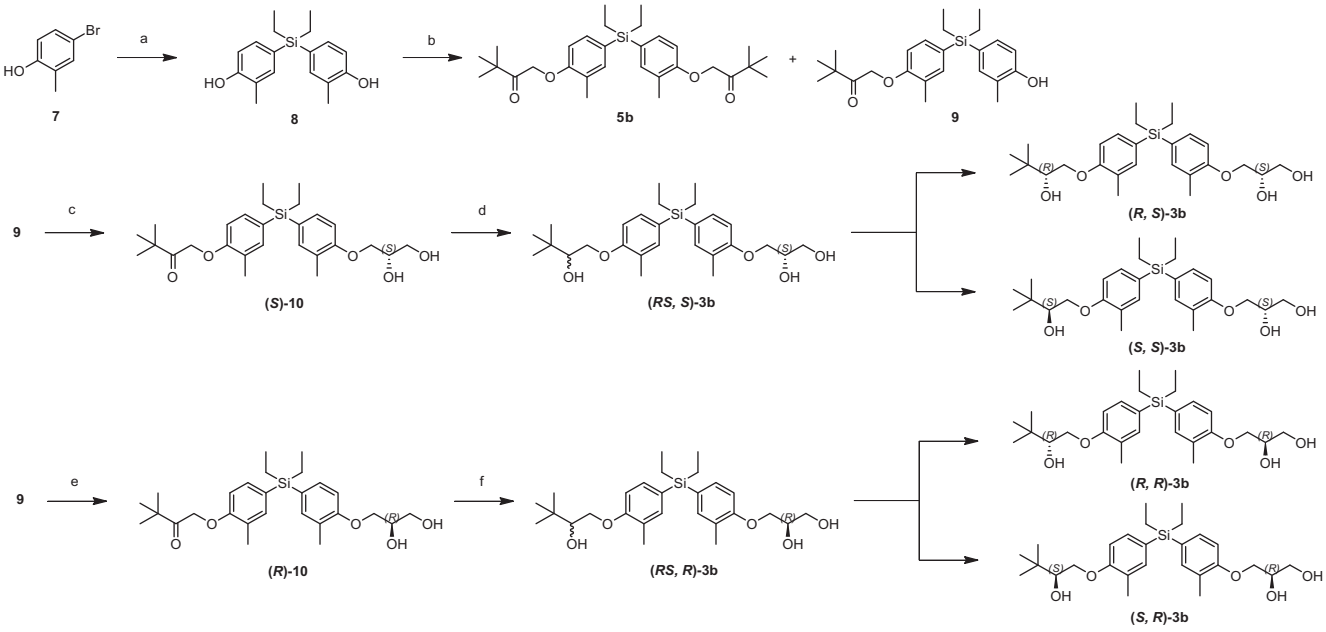
drugs is an attractive approach to find new drug candidates with a clear intellectual property position and has the potential to improve various biological properties, including selectivity, potency, pharmacokinetics, pharmacodynamics and cell penetration.[18–21] Indeed, several organosilicon agents have advanced to clinical studies.[22–25] Therefore, we planned to substitute a silicon atom for a carbon atom in the bis-phenol derivatives with the objective of increasing the selectivity for VDR or AR.

Here, we describe the design and synthesis of organosilicon analogs of bis-phenol derivatives, and evaluation of their biological activities by means of VDR and AR reporter gene assays, as well as SC-3 cell growth inhibition assay (as a measure of androgen-antagonistic activity).

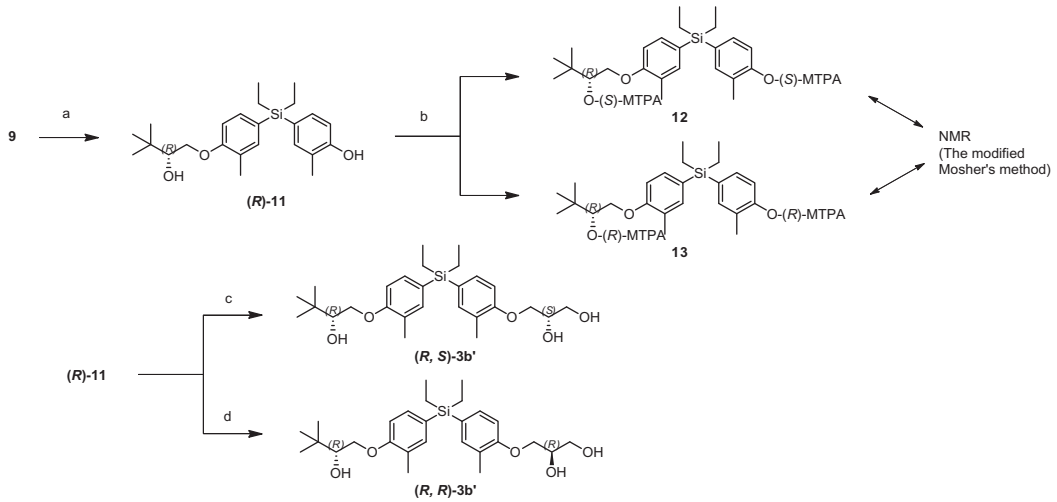
2. Chemistry

Based on our previous work,[16] we first planned to introduce silicon in place of the quaternary carbon in LG190178 (**3a**), which exhibits significant activity in VDR reporter gene assays and in cell growth inhibition assays against various types of cancer cells. Silicon-containing LG190178 analogs were prepared by usual organic synthetic methods, as illustrated in Scheme 1. 4,4′-(Diethylsilanediyl)bis(2-methylphenol) (**8**) was prepared according to the reported method.[26] Briefly, 4-bromo-2-methylphenol (**7**) was reacted with dichlorodiethylsilane in the presence of *n*-butyllithium (*n*-BuLi) in tetrahydrofuran (THF). Compounds **5b** and **9** were prepared by reaction of **8** with 1-chloropinacolone. By the use of an optically pure isoform of glycidol in reactions c and e in Scheme 1, optically pure diol (***S***)**-10** and (***R***)**-10** could be obtained, respectively. Reduction of diol (***S***)**-10** or (***R***)**-10** with sodium borohydride ($NaBH_4$) gave an epimeric mixture of triols (***RS,S***)**-3b** and (***RS,R***)**-3b**, which were separated by chiral HPLC to give pure optical isomers (***R,S***)**-3b**, (***S,S***)**-3b**, (***R,R***)**-3b** and (***S,R***)**-3b**. [In this paper, all structures are drawn so as to put the pivaloyl moiety or its reduced form (if present) on the left side, and the vicinal diol moiety (if present) on the right side. For pure optical isomers of **3b**, the configurations (***S*** or ***R***) of the left- and right-side chains are represented by the first and second letters, respectively, in parentheses before the compound number].

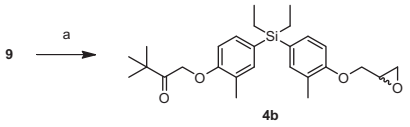
The absolute stereoconfigurations of these compounds were determined by comparison of the HPLC retention times with those of authentic optically pure triols (***R,S***)**-3b′** and (***R,R***)**-3b′**, which were separately prepared by asymmetric synthesis as illustrated in Scheme 2. Specifically, (*R*)-2-methyl-CBS(Corey–Baski–Shibata)-oxazaborolidine-catalyzed asymmetric borane reduction[27] of **9** gave optically active alcohol (***R***)**-11** in 93% ee. The absolute stereoconfiguration of (***R***)**-11** was determined by the modified Mosher's method (NMR) using (+)- or (−)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) esters **12** and **13**.[28] By the use of optically pure isoforms of glycidol, optically pure authentic triols (***R,S***)**-3b′** and (***R,R***)**-3b′**



Scheme 1. Synthesis of the silicon-containing LG190178 analog **3b**. Reagents and conditions: (a) *n*-BuLi, THF, dichlorodiethylsilane, −78 °C then rt, 6 h, 39%; (b) 1-chloropinacolone, sodium hydride (NaH), DMF, 0 °C then rt, 5.5 h, 22% (**5b**), 20% (**9**); (c) (***S***)-glycidol, NaH, DMF, 0 °C then 80 °C, 3.5 h, 46%; (d) $NaBH_4$, MeOH, rt 1 h, 84%; (e) (***R***)-glycidol, NaH, DMF, 0 °C then 80 °C, 3.5 h, 39%; (f) $NaBH_4$, MeOH, rt 1 h, 81%.



Scheme 2. Asymmetric synthesis of (***R,S***)**-3b**′ and (***R,R***)**-3b**′. Reagents and conditions: (a) (***R***)-2-methyl-CBS-oxazaborolidine cat., borane *N*-ethyl-*N*-isopropylaniline complex, THF, 20 °C, 1 h, 92%, 93% ee; (b) (***R***) or (***S***)-MTPA-Cl, pyridine, CH_2Cl_2, rt, 20 h; (c) (***R***)-glycidol, K_2CO_3, acetone, 60 °C, 6 h, 31%, >99% ee; (d) (***S***)-glycidol, K_2CO_3, acetone, 60 °C, 6 h, 20%, >99% ee.



Scheme 3. Synthesis of the silicon-containing LG190176 analog **4b**. Reagents and conditions: (a) epichlorohydrin, NaH, DMF, 0 °C then 120 °C, 3.5 h, 64%.

could be obtained, and their HPLC retention times were consistent with those of (***R,S***)**-3b** and (***R,R***)**-3b**, respectively.

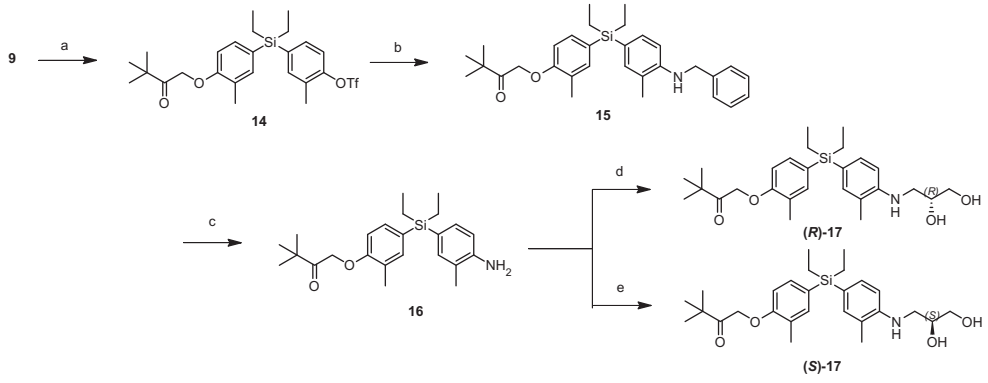
The silicon-containing LG190176 analog **4b** was synthesized by reaction of **9** with epichlorohydrin (Scheme 3). LG190178 (**3a**), LG190176 (**4a**) and LG190155 (**5a**) were prepared according to the reported method.[14]

Next, we planned to prepare the aza-analogs of (***R***)**-10** and (***S***)**-10**, that is (***R***)**-17** and (***S***)**-17**, based on our earlier development studies on nitrogen-containing vitamin D_3 antagonists, DLAMs.[29] Compounds (***S***)**-17** and (***R***)**-17** were prepared by the method illustrated in Scheme 4. Compound **14** was prepared by the triflation of **9.** Buchwald–Hartwig's amination[30,31] reaction of **14** gave **15**. After debenzylation of **15**, optically pure diol (***R***)**-17** and (***S***)**-17** could be obtained by the use of optically pure isoforms of glycidol in reactions d and e in Scheme 4, respectively.

3. Results and discussion

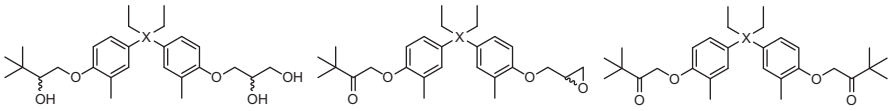
3.1. Reporter gene assay

The selectivities of the synthesized compounds toward VDR and/or AR were evaluated by using reporter gene assay systems. We first compared the activity of LG-compounds and the corresponding silicon analogs (Table 1). 1α,25-Dihydroxyvitamin D_3 (1,25-VD_3) (**1**) showed very potent VDR transcriptional activity with an EC_{50} value of 0.003 μM. In this paper, the VDR transcriptional activity of synthesized compounds is given as PC_{50} value, which is defined as the test chemical concentration estimated to elicit 50% of the positive control (PC) transcription activity obtained with 10 μM 1,25-VD_3 (**1**). LG190178 (**3a**) showed potent VDR transcriptional activity with the PC_{50} value of 0.14 μM. The corresponding silicon compound, that is compound **3b**, also showed rather strong VDR-agonistic activity (PC_{50} = 0.92 μM), but it was less potent than the carba-analog **3a**. The VDR-agonistic activity of LG190178 (**4a**) was also strong (PC_{50} = 0.68 μM), and that of its sila-analog **4b** was only moderate (PC_{50} = 4.8 μM). LG190155 (**5a**) showed moderate VDR-agonistic activity with the PC_{50} value of 4.6 μM, and replacement of the quaternary carbon of LG190155 (**5a**) with a silicon atom, that is, compound **5b**, resulted in disappearance of the VDR-agonistic activity. Overall,



Scheme 4. Synthesis of the aza-analogs (***R***)**-17** and (***S***)**-17**. Reagents and conditions: (a) triflic anhydride, triethylamine, CH_2Cl_2, rt, 1 h, 88%; (b) palladium diacetate, BINAP, Cs_2CO_3, benzylamine, toluene, 100 °C, 6 h, 72%; (c)Pd/C, H_2, EtOH, 61%; (d) (***S***)-glycidol, ethanol, 75 °C, 11 h, 42%; (e) (***R***)-glycidol, ethanol, 75 °C, 11 h, 47%.

Table 1
The results of VDR and AR reporter gene assays of LG-compounds



Compound	X =	VDR PC_{50} (μM)[a,c]	AR IC_{50}[b,c] (μM) (inhibition% at 10 μM)	VDR(PC_{50})/AR(IC_{50})[d]
LG190178 (**3a**)[e]	C	0.14	>>10 (16%)	<0.014
3b[e]	Si	0.92	6.8	0.14
LG190176 (**4a**)[f]	C	0.68	>>10 (12%)	<0.068
4b[f]	Si	4.8	>10 (49%)	ca.0.48
LG190155 (**5a**)	C	4.6	>10 (44%)	<0.46
5b	Si	>30	6.2	>4.8
Hydroxyflutamide	—	Inactive[g]	0.3	—
1,25-VD_3 (**1**)	—	0.003 (EC_{50})	>10 (45%)	—

[a] VDR transcriptional activity.
[b] AR transcription-inhibitory activity.
[c] Data are the means of three experiments.
[d] VDR(PC_{50})/AR(IC_{50}) was defined as VDR transcriptional activity (PC_{50} value)/AR transcription-inhibitory activity (IC_{50} value).
[e] Diastereomeric mixture.
[f] Enantiomeric mixture.
[g] No activity was observed in the concentration range examined.

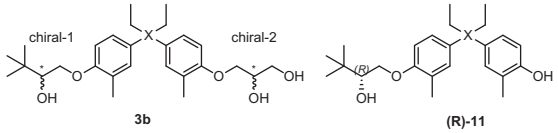
therefore, C/Si exchange of compounds **3**-**5** reduced the VDR-agonistic activity.

None of the compounds listed in Table 1 showed AR-agonistic activity, as evaluated by AR reporter gene assay in the presence of testosterone (0.3 nM). Hydroxyflutamide, which is a well-known androgen antagonist, showed strong AR transcription-inhibitory activity with the IC_{50} value of 0.3 μM. The AR-antagonistic activities of carbon compounds **3a**, **4a** and **5a** were all weak with IC_{50} values larger than 10 μM. Interestingly, the corresponding silicon compounds, that is, compounds **3b**, **4b** and **5b**, exhibited higher AR-antagonistic activities than **3a**, **4a** and **5a**, respectively. A comparison of the results of VDR and AR reporter gene assays revealed that the introduction of the silicon atom into the bis-phenol skeleton enhanced AR-antagonistic activity and reduced VDR-agonistic activity. In consequence, the AR selectivities (VDR/AR value) of silicon-containing compounds **3b**, **4b** and **5b** were higher than that of the corresponding carbon compounds.

Since the silicon-containing LG190178 analog, that is compound **3b**, showed higher AR selectivity than LG190178 (**3a**), we next evaluated optically pure isomers of **3b** and (***R***)**-11** in the same manner as described above. The results are shown in Table 2. In the VDR reporter gene assay, (***R***,***S***)**-3b** showed the strongest activity with the PC_{50} value of 0.81 μM. Its antipode, that is, compound (***S***,***R***)**-3b**, showed the weakest activity (PC_{50} >10 μM). This tendency was consistent with that of the VDR binding affinities of LG190178 stereo-isomers.[16] Deletion of the vicinal diol moiety on the right side of (***R***,***S***)**-3b** (compound (***R***)**-11**) resulted in a decrease of VDR-agonistic activity. The AR-antagonistic activities of these optical isomers were moderate (IC_{50} = 5.8–7.4 μM), and the IC_{50} value of compound (***R***)**-11** was higher than 10 μM. As a result, (***S***,***R***)**-3b** exhibited the highest AR selectivity among the isomers of **3b**, and its AR selectivity (VDR/AR value) was more than 100 times greater than that of LG190178 (**3a**).

Next, the VDR-agonistic/AR-antagonistic activity ratios of compounds (***R***)**-** and (***S***)**-10** and aza-analogs (***R***)**-** and (***S***)**-17** were evaluated (Table 3). Compound (***S***)**-17** showed moderate VDR transcriptional activity with the PC_{50} value of 2.5 μM. Its antipode (***R***)**-17** and compounds (***R***)**-** and (***S***)**-10** also showed moderate VDR-agonistic activity with PC_{50} values of 2.0–7.0 μM. In the AR reporter gene assay, compound (***R***)**-10** showed moderate AR transcription-inhibitory activity with the IC_{50} value of 4.0 μM. On the other hand, the IC_{50} values of other compounds were higher than 10 μM.

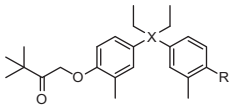
Table 2
Results of VDR and AR reporter gene assays of optically pure isomers of **3b** and compound (***R***)**-11**

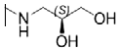
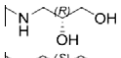
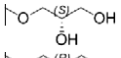
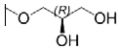


Compound	X =	VDR PC_{50}[a,c] (μM)	AR IC_{50}[b,c] (μM) (inhibition% at 10 μM)	VDR(PC_{50})/AR(IC_{50})[d]
(***R***,***S***)-**3b**[e]	Si	0.81	5.8	0.14
(***S***,***S***)-**3b**[e]	Si	2.2	8.3	0.27
(***R***,***R***)-**3b**[e]	Si	2.1	6.7	0.31
(***S***,***R***)-**3b**[e]	Si	>10	7.4	>1.4
(***R***)-11	Si	8.2	>10 (47%)	—

[a] VDR transcriptional activity.
[b] AR transcription-inhibitory activity.
[c] Data are the means of three experiments.
[d] VDR(PC_{50})/AR(IC_{50}) was defined as VDR transcriptional activity (PC_{50} value)/AR transcription-inhibitory activity (IC_{50} value).
[e] The chiralities are indicated as (chiral-1, chiral-2).

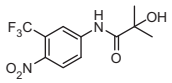
Table 3
Results of VDR and AR reporter gene assays of compounds (***R***)- and (***S***)**-10** and aza-analogs (***R***)**-** and (***S***)**-17**

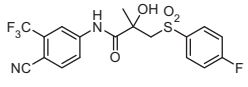


Compound	X =	R =	VDR PC_{50}[a,c] (μM)	AR IC_{50}[b,c] (μM) (inhibition % at 10 μM)	VDR(PC_{50})/AR(IC_{50})[d]
(***S***)**-17**	Si		2.5	>10 (44%)	–
(***R***)**-17**	Si		7.0	>10 (38%)	–
(***S***)**-10**	Si		2.0	>10 (44%)	–
(***R***)**-10**	Si		3.7	4.0	0.93

[a] VDR transcriptional activity.
[b] AR transcription-inhibitory activity.
[c] Data are the means of three experiments.
[d] VDR(PC_{50})/AR(IC_{50}) was defined as VDR transcriptional activity (PC_{50} value)/AR transcription-inhibitory activity (IC_{50} value).

Table 4
Androgen-antagonistic activity


Hydroxyflutamide


Bicalutamide

Compound	SC-3 IC_{50}[a] (μM)
(***S***,***R***)**-3b**	0.072
(***R***)**-10**	0.113
Hydroxyflutamide	1.4
Bicalutamide	3.0

[a] Inhibitory activity on testosterone-induced cell growth of androgen-dependent cell line SC-3. Data are the means of three experiments.

3.2. Cell growth-inhibitory activity assay as a measure of androgen-antagonistic activity

Androgen-antagonistic activities of representative AR-selective ligands were evaluated in terms of inhibitory activity on testosterone-induced cell growth of androgen-dependent mouse mammary carcinoma cell line SC-3.[32,33] As shown in Table 4, (***S***,***R***)**-3b**, which exhibited the highest AR selectivity among the stereo-isomers of the silicon-introduced LG190178 analog **3b**, showed strong anti-androgen activity with the IC_{50} value of 0.072 μM. It was 20 times more potent than the well-known androgen antagonist, hydroxyflutamide (IC_{50} = 1.4 μM). Compound (***R***)**-10** also showed strong activity with an IC_{50} value of 0.113 μM.

4. Conclusion

We designed and synthesized silicon-containing bis-phenol derivatives with the aim of increasing the selectivity of the compounds for VDR or AR, since we had previously found that bis-phenol derivatives showed androgen-antagonistic activity, and the selectivity could be changed by modifying the structure.[16,17] The results of VDR and AR reporter gene assays revealed that substitution of the silicon atom for carbon in the bis-phenol skeleton generally enhanced AR activity and reduced VDR activity. In consequence, the AR selectivity of the silicon-containing compounds was higher than that of corresponding carbon compounds. To our knowledge, this is the first report of nuclear receptor (NR) selectivity switching by sila-substitution (C/Si exchange). Compound (***S***,***R***)**-3b**, which exhibited the highest AR selectivity among the isomers of the silicon-containing LG190178 analog **3b**, showed strong anti-androgenic activity with an IC_{50} value of 0.072 μM in SC-cell proliferation-inhibitory assay. It is 20 times more potent than the well-known androgen antagonist, hydroxyflutamide (IC_{50} = 1.4 μM). Our results suggest that sila-substitution (C/Si exchange) is a useful approach for structural development of AR-selective ligands.

5. Experimental

5.1. Chemistry

5.1.1. General

^{1}H NMR spectra were recorded on a JEOL JNM-GX500 and JNM-ECA-500 (500 MHz) spectrometer. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm) downfield from tetramethylsilane (*d*) and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet, br = broad. Chemical shifts for ^{13}C NMR are reported in ppm relative to the centerline of the triplet at 77.0 ppm for deuteriochloroform. Mass spectra were recorded on a JEOL JMS-HX110 spectrometer. Melting points were determined on a MP-J3 melting point apparatus (Yanaco, Japan). Routine thin layer chromatography (TLC) and preparative TLC (PTLC) were performed on silica gel 60 F254 plates (Merck, Germany). Flash column chromatography was performed on Silica gel 60 (spherical, particle size 40–100 μm; Kanto).The purity of tested compounds was determined by ultra-high-performance liquid chromatography (UHPLC (Nexera system, Shimadzu, Japan)) [YMC-UltraHT Hydrosphre C18 column (75 × 3.0 mm I.D. S-3, 12 nm), 20–90% acetonitrile in H_2O with 0.1% phosphoric acid for 8.5 min, 0.8 mL/min, 40 °C, UV detection: 254 nm]. All tested compounds showed >95% purity in UHPLC (see Supplementary data).

5.1.2. 3-(4-(3-(4-(2-Hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)pentan-3-yl)-2-methylphenoxy)propane-1,2-diol LG190178 (3a)

LG190178 (**3a**) was prepared according to the reported method.[14] ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.96–6.94 (m, 2H), 6.91–6.89 (m, 2H), 6.70 (d, 2H, *J* = 8.5 Hz), 4.12–4.07 (m, 2H), 4.03 (d, 2H, *J* = 4.9 Hz), 3.87–3.84 (m, 2H), 3.77 (dd, 1H, *J* = 5.5, 11.6 Hz), 3.70 (d, 1H, *J* = 8.5 Hz), 2.17 (s, 3H), 2.16 (s, 3H), 2.04 (q, 4H, *J* = 7.3 Hz), 1.01 (s, 18H), 0.59 (t, 6H, *J* = 7.3 Hz). ^{13}C NMR (500 MHz, $CDCl_3$): δ 154.32, 154.01, 141.41, 141.09, 130.66,

130.63, 126.24, 126.12, 125.51, 125.38, 110.13, 110.10, 77.31, 70.47, 69.22, 63.90, 48.44, 33.56, 29.29, 26.05, 16.59, 16.52, 14.17, 8.42. MS (FAB+) *m*/*z*: 485 (M^+).

5.1.3. 3,3-Dimethyl-1-(2-methyl-4-(3-(3-methyl-4-(oxiran-2-ylmethoxy)phenyl)pentan-3-yl)phenoxy)butan-2-one: LG190176 (4a)

LG190176 (**4a**) was prepared according to the reported method.[14] ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.93–6.88 (m, 4H), 6.67 (d, 1H, *J* = 8.4 Hz), 6.49 (d, 1H, *J* = 8.4 Hz), 4.83 (s, 2H), 4.18 (dd, 1H, *J* = 3.4, 9.4 Hz), 3.95 (dd, 1H, *J* = 5.4, 11.0 Hz), 3.37–3.34 (m, 1H), 2.90–2.89 (m, 1H), 2.78–2.77 (m, 1H), 2.23 (s, 3H), 2.19 (s, 3H), 2.00 (q, 4H, *J* = 7.3 Hz), 1.25 (s, 18H), 0.58 (t, 6H, *J* = 7.3 Hz). MS (FAB+) *m*/*z:* 438 (M^+).

5.1.4. 1,1′-((Pentane-3,3-diylbis(2-methyl-4,1-phenylene))bis(oxy))bis(3,3-dimethylbutan-2-one): LG190155 (5a)

LG190155 (**5a**) was prepared according to the reported method.[14] white solid, mp: 106–108 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27–7.25 (m, 2H), 6.89 (d, 2H, *J* = 8.5 Hz), 6.49 (d, 2H, *J* = 8.5 Hz), 4.83 (s, 2H), 2.23 (s, 6H), 2.00 (q, 4H, *J* = 7.3 Hz), 1.24 (s, 18H), 0.58 (t, 6H, *J* = 7.3 Hz). ^{13}C NMR (500 MHz, $CDCl_3$): δ 210.01, 153.99, 141.44, 130.77, 126.09, 125.95, 110.18, 69.62, 48.46, 43.22, 29.31, 26.35, 16.62, 8.49. MS (FAB+) *m*/*z:* 480 (M^+).

5.1.5. 1-(4-(3-(4-Hydroxy-3-methylphenyl)pentan-3-yl)-2-methylphenoxy)-3,3-dimethylbutan-2-one (6a)

Compound **6a** was prepared according to the reported method.[14] Pale yellow paste. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91–6.88 (m, 3H), 6.83 (d, 1H, *J* = 7.9 Hz), 6.63 (d, 1H, *J* = 7.9 Hz), 6.49 (d, 1H, *J* = 7.9 Hz), 4.83 (s, 2H), 2.22 (s, 6H), 2.00 (q, 4H, *J* = 6.7 Hz), 1.24 (s, 9H), 0.58 (t, 6H, *J* = 6.7 Hz). ^{13}C NMR (500 MHz, $CDCl_3$): δ 210.36, 153.90, 151.39, 141.59, 140.84, 130.74, 130.54, 126.58, 126.02, 125.94, 122.54, 113.99, 110.15, 69.58, 48.39, 43.20, 29.29, 26.31, 16.58, 16.62, 8.40. MS (FAB+) *m*/*z:* 382 (M+).

5.1.6. 4,4′-(Diethylsilanediyl)bis(2-methylphenol) (8)

To a solution of 4-bromo-o-cresol (**7**) (6.0 g, 32 mmol) in dry tetrahydrofuran (36 mL) was added *n*-butyl lithium in *n*-hexane (2.69 M, 27.6 mL, 75.6 mmol) under an Ar atmosphere at −78 °C. The mixture was stirred at the same temperature for 1 h, and then added to a solution of dichlorodiethylsilane (1.6 mL, 10.6 mmol) in dry tetrahydrofuran (1.6 mL) at −78 °C, and stirring was continued at room temperature for 5.5 h. The reaction was quenched with NH_4Cl aq, and the whole was extracted with ethyl acetate. The extract was successively washed with water and brine, and then dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by means of silica gel column chromatography (hexane/ethyl acetate = 9/1 to 5/1) to give **8** (1.24 g, 39.1%) as a white solid. mp: 110–112 °C, ^{1}H NMR (500 MHz, CD_3OD): δ 7.15 (s, 2H), 7.11 (d, 2H, *J* = 7.9 Hz), 6.73 (d, 2H, *J* = 7.9 Hz), 2.16 (s, 6H), 0.96–0.94 (m, 10H). ^{13}C NMR (500 MHz, CD_3OD): δ 157.51, 138.54, 134.85, 127.19, 124.92, 115.21, 16.22, 7.85, 5.32. MS (FAB+) *m*/*z*: 300 (M^+).

5.1.7. 1,1′-(((Diethylsilanediyl)bis(2-methyl-4,1-phenylene))bis(oxy))bis(3,3-dimethylbutan-2-one) (5b) and 1-(4-(diethyl(4-hydroxy-3-methylphenyl)silyl)-2-methylphenoxy)-3,3-dimethylbutan-2-one (9)

To a solution of **8** (1.03 g, 3.43 mmol) in dry *N*,*N*-dimethylformamide (8 mL) was added sodium hydride (137 mg of a 60% suspension in mineral oil, 3.43 mmol) and *N*,*N*-dimethylformamide (2 mL) at 0 °C. The mixture was stirred at the same temperature for 0.5 h. To this was added 1-chloropinacolone (0.45 mL, 3.43 mmol), and stirring was continued at room temperature for 5 h. The reaction was quenched with H_2O, and the whole was extracted with ethyl acetate. The extract was successively washed with water and brine, and then dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by means of silica gel column chromatography (hexane/ethyl acetate = 9/1) to give **5b** (347 mg, 20.4%) and **9** (304 mg, 22.2%). **5b:** white solid, mp: 99–100 °C,[1] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (s, 2H), 7.22 (d, 2H, *J* = 7.9 Hz), 6.59 (d, 2H, *J* = 7.9 Hz), 4.87 (s, 4H), 2.28 (s, 6H), 1.26 (s, 18H), 1.01–0.97 (m, 10H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 209.67, 157.18, 137.51, 133.80, 128.00, 126.43, 110.41, 69.17, 43.20, 26.34, 16.40, 7.45, 4.18. MS (FAB+) *m*/*z*: 497(M^+). Compound **9**: White solid, mp: 117–119 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26–7.22 (m, 2H), 7.19 (d, 1H, *J* = 7.9 Hz), 6.76 (d, 1H, *J* = 7.9 Hz), 6.59 (d, 1H, *J* = 7.9 Hz), 4.87 (s, 2H), 2.28 (s, 3H), 2.23 (s, 3H), 1.26 (s, 9H), 1.01–0.95 (m, 10H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 209.84, 157.20, 154.82, 137.71, 137.52, 134.12, 133.77, 128.13, 127.52, 126.46, 123.09, 114.51, 110.42, 69.18, 43.20, 26.34, 16.40, 15.70, 7.46, 4.20. MS (FAB+) *m*/*z:* 398 (M^+).

5.1.8. (*S*)-1-(4-((4-(2,3-Dihydroxypropoxy)-3-methylphenyl)diethylsilyl)-2-methylphenoxy)-3,3-dimethylbutan-2-one((*S*)-10)

To a solution of **9** (245 mg, 0.62 mmol) in dry *N*,*N*-dimethylformamide (3 mL) was added sodium hydride (27 mg of a 60% suspension in mineral oil, 0.68 mmol) at 0 °C, and the mixture was stirred at the same temperature for 0.5 h. To this was added (*S*)-glycidol (0.044 mL, 0.68 mmol), and stirring was continued at 80 °C for 3 h. The reaction was quenched with H_2O, and the whole was extracted with ethyl acetate. The extract was successively washed with water and brine, and then dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by means of silica gel column chromatography (hexane/ethyl acetate = 4/1 to 1/1) to give (***S***)**-10** (134 mg, 46.2%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29–7.22 (m, 4H), 6.81 (d, 1H, *J* = 7.9 Hz), 6.59 (d, 1H, *J* = 7.9 Hz), 4.87 (s, 2H), 4.14–4.10 (m, 1H), 4.05 (d, 2H, *J* = 4.9 Hz), 3.85 (dd, 1H, *J* = 3.7, 11.0 Hz), 3.76 (dd, 1H, *J* = 5.5, 11.0 Hz), 2.28 (s, 3H), 2.21 (s, 3H), 1.25 (s, 9H), 1.02–0.97 (m, 10H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 209.78, 157.30, 157.16, 137.47, 137.27, 134.02, 133.73, 127.97, 127.77, 126.42, 125.87, 110.49, 110.41, 70.43, 69.12, 68.85, 63.80, 43.20, 26.30, 16.37, 16.26, 7.42, 4.14. HRMS (FAB+) *m*/*z*: calcd for $C_{27}H_{40}O_5Si$ 472.2645, found 472.2654 (M^+).

5.1.9. (*R*)-1-(4-((4-(2,3-Dihydroxypropoxy)-3-methylphenyl)diethylsilyl)-2-methylphenoxy)-3,3-dimethylbutan-2-one((*R*)-10)

The title compound was prepared according to the procedure described for (***S***)**-10**, starting from compound **9** and (*R*)-glycidol. (132 mg, 39.1%), NMR spectra were the same as those of (***S***)**-10**. HRMS (FAB+) *m*/*z:* calcd for $C_{27}H_{40}O_5Si$ 472.2645, found 472.2671 (M^+).

5.1.10. (2*S*)-3-(4-(Diethyl(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)silyl)-2-methylphenoxy)propane-1,2-diol [diastereomeric mixture] ((***RS***,***S***)-3b)

To a solution of (***S***)**-10** (103 mg, 0.22 mmol) in methanol (2 mL) was added sodium borohydride (9.9 mg, 0.26 mmol) and methanol (1 mL) at 0 °C. The mixture was stirred at room temperature for 1 h. The reaction was quenched with NH_4Cl aq, and the whole was extracted with ethyl acetate. The extract was successively washed with water and brine, and then dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by means of silica gel column chromatography (hexane/ethyl acetate = 2/1) to give (***RS***,***S***)**-3b** (86.6 mg, 84.1%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (d, 2H, *J* = 7.9 Hz), 7.25 (s, 2H), 6.81 (d, 2H, *J* = 7.9 Hz), 4.12 (dd, 1H, *J* = 3.1, 9.2 Hz), 4.06 (d, 2H, *J* = 4.9 Hz), 3.91–3.84 (m, 2H), 3.78 (dd, 1H, *J* = 5.5, 11.0 Hz), 3.72 (d, 1H, *J* = 8.5 Hz), 2.22 (s, 3H), 2.21 (s, 3H), 1.01 (s, 9H), 1.01–098 (m, 10H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 157.63, 157.30, 137.33, 137.30, 134.06, 133.98, 127.94,

127.54, 126.03, 125.91, 110.62, 110.53, 77.26, 70.43, 69.11, 68.96, 63.83, 33.61, 26.05, 16.39, 16.31, 7.46, 4.17. HRMS (FAB+) *m*/*z*: calcd for $C_{27}H_{43}O_5Si$ 475.2880, found 475.2871 ($M+H^+$).

5.1.11. (2*R*)-3-(4-(Diethyl(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)silyl)-2-methylphenoxy)propane-1,2-diol [diastereomeric mixture] ((*RS*,*R*)-3b)

The title compound was prepared according to the procedure described for (***RS***,***S***)**-3b**, starting from compound (***R***)**-10** (78.7 mg, 81.0%). NMR spectra were the same as those of (***RS***,***S***)**-3b**. HRMS(FAB+) *m*/*z:* calcd for $C_{27}H_{43}O_5Si$ 475.2880, found 475.2876 ($M+H^+$).

5.1.12. (*S*)-3-(4-(Diethyl(4-((*R*)-2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)silyl)-2-methylphenoxy)propane-1,2-diol ((*R*,*S*)-3b) and (*S*)-3-(4-(diethyl(4-((*S*)-2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)silyl)-2-methylphenoxy)propane-1,2-diol ((*S*,*S*)-3b)

The diastereomeric mixture (***RS***,***S***)**-3b** was separated by chiral HPLC [Chiralpak IA (4.6 × 250 mm, IPA/hexane = 15/85), 1.0 mL/min, 20 °C]. (***R***,***S***)**-3b**: NMR spectra were the same as those of (***RS***,***S***)**-3b**. HRMS (FAB+): calcd for $C_{27}H_{43}O_5Si$ 475.2880, found 475.2883 ($M+H^+$). HPLC: Chiralpak IA (4.6 × 250 mm, IPA/hexane = 15/85), 0.5 mL/min, 20 °C, retention time = 18.4 min, >99%ee. (***S***,***S***)**-3b**: NMR spectra were the same as those of (***RS***,***S***)**-3b**. HRMS (FAB+): calcd for $C_{27}H_{43}O_5Si$ 475.2880, found 475.2876 ($M+H^+$). HPLC: Chiralpak IA (4.6 × 250 mm, IPA/hexane = 15/85), 0.5 mL/min, 20 °C, retention time = 35.8 min, >99%ee.

5.1.13. (*R*)-3-(4-(Diethyl(4-((*R*)-2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)silyl)-2-methylphenoxy)propane-1,2-diol ((*R*,*R*)-3b) and (*R*)-3-(4-(diethyl(4-((*S*)-2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)silyl)-2-methylphenoxy)propane-1,2-diol((*S*,*R*)-3b)

The diastereomeric mixture (***RS***,***R***)**-3b** was separated by chiral HPLC [Chiralpak IA (4.6 × 250 mm, IPA/hexane = 1/4), 1.0 mL/min, 20 °C]. (***R***,***R***)**-3b**: NMR spectra were the same as those of (***RS***,***R***)**-3b**. HRMS (FAB+): calcd for $C_{27}H_{43}O_5Si$ 475.2880, found 475.2883 ($M+H^+$). HPLC: Chiralpak IA (4.6 × 250 mm, IPA/hexane = 15/85), 0.5 mL/min, 20 °C, retention time = 17.8 min, >99%ee. (***S***,***R***)**-3b**: NMR spectra were the same as those of (***RS***,***R***)**-3b**. HRMS (FAB+): calcd for $C_{27}H_{43}O_5Si$ 475.2880, found 475.2880 ($M+H^+$). HPLC: Chiralpak IA (4.6 × 250 mm, IPA/hexane = 15/85), 0.5 mL/min, 20 °C, retention time = 38.0 min, >99%ee.

5.1.14. 3-(4-(Diethyl(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)silyl)-2-methylphenoxy)propane-1,2-diol [diastereomeric mixture] (3b)

A diastereomeric mixture **3b** was prepared by mixing equal amounts of pure optical isomers (***R***,***S***)**-3b**, (***S***,***S***)**-3b**, (***R***,***R***)**-3b** and (***S***,***R***)**-3b**.

5.1.15. 1-(4-(Diethyl(3-methyl-4-(oxiran-2-ylmethoxy)phenyl)silyl)-2-methylphenoxy)-3,3-dimethylbutan-2-one (4b)

To a solution of **9** (149 mg, 0.37 mmol) in dry *N*,*N*-dimethylformamide (2 mL) was added sodium hydride (15 mg of a 60% suspension in mineral oil, 0.40 mmol) at 0 °C, and the mixture was stirred at the same temperature for 0.5 h. To this was added epichlorohydrin (0.029 mL, 0.40 mmol), and stirring was continued at 120 °C for 3 h. The reaction was quenched with H_2O, and the whole was extracted with ethyl acetate. The extract was successively washed with water and brine, and then dried over $MgSO_4$. The solvent was evaporated, and the residue was purified silica gel column chromatography (hexane/ethyl acetate = 9/1) to give **4b** (108 mg, 63.6%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.27–7.21 (m, 4H), 6.79 (d, 2H, *J* = 8.0 Hz), 6.59 (d, 2H, *J* = 8.0 Hz), 4.87(s, 2H), 4.24–4.21 (m, 1H), 4.00–3.97 (m, 1H), 3.38–3.35 (m, 1H), 2.90 (dd, 1H, *J* = 4.0, 5.0 Hz), 2.77 (dd, 1H, *J* = 3.0, 5.0 Hz), 2.28 (s, 3H), 2.23 (s, 3H),1.01–0.97 (m, 19H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 209.83, 157.59, 157.27, 137.61, 137.41, 134.03, 133.87, 128.13, 12.73, 126.54, 126.35, 110.63, 110.50, 69.26, 68.46, 50.40, 44.79, 43.34, 26.45, 16.53, 16.37, 7.57, 4.27. HRMS (FAB+) *m*/*z*: calcd for $C_{27}H_{38}O_4Si$ 454.2539, found 454.2542 (M^+).

5.1.16. 4-((4-(3,3-Dimethyl-2-oxobutoxy)-3-methylphenyl) diethylsilyl)-2-methylphenyl trifluoromethanesulfonate (14)

To a solution of **9** (366 mg, 0.92 mmol) in dichloromethane (3 mL) was added triethylamine (0.19 mL, 1.4 mmol) and trifluoromethanesulfonic anhydride (0.19 mL, 1.1 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h and then evaporated, and the residue was purified by means of silica gel column chromatography (hexane/ethyl acetate = 9/1) to give a solid of **14** (427 mg, 87.5%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.38 (s, 1H), 7.35 (d, 1H, *J* = 7.9 Hz), 7.24–7.18 (m, 2H), 7.19 (s, 1H), 6.60 (d, 1H, *J* = 7.9 Hz), 4.89 (s, 2H), 2.36 (s, 3H), 2.30 (s, 3H), 1.26 (s, 9H), 1.04–0.96 (m, 10H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 209.69, 157.54, 149.39, 138.63, 137.96, 137.41, 134.20, 133.77, 129.76, 126.81, 126.52, 120.37, 110.56, 69.07, 43.21, 26.36, 16.42, 16.34, 7.32, 3.91. MS (FAB+) *m*/*z:* 530 (M^+).

5.1.17. 1-(4-((4-(Benzylamino)-3-methylphenyl)diethylsilyl)-2-methylphenoxy)-3,3-dimethylbutan-2-one (15)

To a mixture of cesium carbonate (468 mg, 1.44 mmol), palladium diacetate (13.9 mg, 0.06 mmol) and (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) (57.6 mg, 0.09 mmol) was added a mixture of **14** (327 mg, 0.62 mmol), benzylamine (0.135 mL, 1.23 mmol) and toluene (2 mL) under an Ar atmosphere at room temperature. The reaction mixture was stirred at the same temperature for 0.5 h and at 100 °C for 6 h, and then filtered through a Celite pad. The filtrate was evaporated and the residue was purified by means of silica gel column chromatography (hexane/ethyl acetate = 20/1) to give **15** (216 mg, 71.8%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.40–7.34 (m, 4H), 7.30–7.22 (m, 4H), 7.19 (s, 1H), 6.62 (d, 1H, *J* = 7.9 Hz), 6.59 (d, 1H, *J* = 8.5 Hz), 4.86 (s, 2H), 4.37 (s, 2H), 2.28 (s, 3H), 2.14 (s, 3H), 1.26 (s, 9H), 0.99–0.97 (m, 10H). ^{13}C NMR (500 MHz, CDCl3): δ 209.67, 157.07, 146.86, 139.41, 137.57, 136.55, 164.36, 133.57, 136.55, 134.36, 133.80, 128.66, 127.61, 127.30, 126.33, 122.58, 121.18, 110.39, 109.43, 69.24, 48.16, 43.20, 16.35, 17.57, 16.40, 7.55, 4.31. MS (FAB+) *m*/*z*: 487 (M^+).

5.1.18. 1-(4-((4-Amino-3-methylphenyl)diethylsilyl)-2-methylphenoxy)-3,3-dimethylbutan-2-one (16)

To a solution of **15** (195 mg, 0.40 mmol) in ethanol (3 mL) was added Pd/C (5%, 10 mg) at room temperature. The mixture was stirred at the same temperature for 12 h and then filtered through a Celite pad. The filtrate was evaporated and the residue was purified by means of silica gel column chromatography (hexane/ethyl acetate = 9/1) to give crude **16** (96.4 mg, 60.8%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.27–7.11 (m, 2H), 7.15(s, 2H), 6.66 (d, 2H, *J* = 7.9 Hz), 6.59 (d, 2H, *J* = 7.9 Hz), 4.86 (s, 2H), 2.28 (s, 3H), 2.14 (s, 3H), 1.25 (s, 9H), 0.96–0.94 (m, 10H). MS (FAB+) *m*/*z*: 397 (M^+).

5.1.19. (*S*)-1-(4-((4-((2,3-Dihydroxypropyl)amino)-3-methylphenyl)diethylsilyl)-2-methylphenoxy)-3,3-dimethylbutan-2-one((*S*)-17)

To a solution of crude **16** (38.1 mg, 0.10 mmol) in ethanol (0.4 mL) was added (*R*)-glycidol (0.044 mL, 0.68 mmol) at room temperature. The mixture was stirred at 75 °C for 11 h and at room temperature for 11 h, and then evaporated. The residue was purified by PTLC (hexane/ethyl acetate = 1/1) to give (***S***)**-17** (19.2 mg, 42.0%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.26–7.23 (m, 2H), 7.16 (s, 1H), 6.64 (d, 1H, *J* = 7.9 Hz), 6.59 (d, 1H,

J = 7.9 Hz), 4.87 (s, 2H), 4.02–4.00 (m, 1H), 3.80 (dd, 1H, J = 3.4, 11.3 Hz), 3.66 (dd, 1H, J = 5.3, 11.3 Hz), 3.35 (dd, 1H, J = 4.0, 13.1 Hz), 3.26– m, 1H), 2.28 (s, 3H), 2.14 (s, 3H), 1.25 (s, 9H), 0.99–0.97 (m, 10H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 209.67, 157.07, 146.73, 137.55, 136.74, 134.30, 133.78, 128.55, 126.35, 123.25, 121.94, 110.40, 109.59, 70.21, 69.21, 64.89, 46.29, 43.19, 26.34, 17.53, 16.40, 7.52, 4.27. HRMS (FAB+) m/z: calcd for $C_{27}H_{43}NO_4Si$ 472.2883, found 475.2892 ($M+H^+$).

5.1.20. (*R*)-1-(4-((4-((2,3-Dihydroxypropyl)amino)-3-methylphenyl)diethylsilyl)-2-methylphenoxy)-3,3-dimethylbutan-2-one((*R*)-17)

The title compound was prepared according to the procedure described for (***S***)**-17**, starting from compound **16** and (*S*)-glycidol (21.5 mg, 47.0%). NMR spectra were the same as those of (***S***)**-17**. HRMS(FAB+) m/z: calcd for $C_{27}H_{43}NO_4Si$ 472.2883, found 475.2888 ($M+H^+$).

5.1.21. (*R*)-4-(Diethyl(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)silyl)-2-methylphenol((*R*)-11)

To a solution of **9** (104 mg, 0.26 mmol) in dry tetrahydrofuran (1.5 mL) was added a mixture of (*R*)-2-methyl-CBS-oxazaborolidine (1 M solution in toluene, 0.026 mL), borane *N*-ethyl-*N*-isopropylaniline complex (2 M solution in tetrahydrofuran, 0.156 mL) and dry tetrahydrofuran (1.5 mL) at 20 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h. The reaction was quenched with NH_4Cl aq, and the whole was evaporated. The residue was purified by means of silica gel column chromatography (hexane/ethyl acetate = 20/1 to 4/1) to give (***R***)**-11** (95.8 mg, 92.0%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30–7.19 (m, 4H), 6.83 (d, 2H, J = 8.0 Hz), 6.76 (d, 2H, J = 8.0 Hz), 4.14 (dd, 1H, J = 3.0, 9.5 Hz), 3.92 (dd, 1H, J = 9.5, 8.5 Hz), 3.74 (dd, 1H, J = 3.0, 8.5 Hz), 2.24 (s, 3H), 2.23 (s, 3H),1.03 (s, 9H), 1.01–0.97 (m, 10H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 157.67, 154.95, 137.82, 137.43, 134.20, 134.11, 127.80, 127.56, 126.11, 123.32, 114.61, 110.69, 77.45, 69.15, 33.73, 26.17, 16.52, 15.86, 7.59, 4.32. HRMS (FAB+): calcd for $C_{24}H_{37}O_3Si$ 401.2515, found 401.2503 ($M+H^+$). HPLC: Chiralpak IA (4.6 x 250 mm, IPA/hexane = 15/85), 0.5 mL/min, 20 °C, retention time = 13.1 min, 93%ee. ((*S*)-4-(Diethyl(4-(2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)silyl)-2-methylphenol: retention time = 33.9 min).

5.1.22. (*R*)-3-(4-(Diethyl(4-((*R*)-2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)silyl)-2-methylphenoxy)propane-1,2-diol ((*R*,*R*)-3b′)

To a mixture of (***R***)**-11** (19.2 mg, 0.05 mmol), K_2CO_3 (9.9 mg, 0.07 mmol) and acetone (0.2 mL) was added (*R*)-glycidol (0.046 ml, 0.07 mmol) at room temperature. The mixture was stirred at 60 °C for 6 h and at room temperature for 16 h, and then evaporated. The residue was purified by PTLC (hexane/ethyl acetate = 1/1) to give (***R***,***R***)**-3b′** (7.1 mg, 31.3%) as a colorless oil. NMR spectra were the same as those of (***RS***,***S***)**-3b**. HRMS (FAB+): calcd for $C_{27}H_{43}O_5Si$ 475.2880, found 475.2890 ($M+H^+$). HPLC: Chiralpak IA (4.6 × 250 mm, IPA/hexane = 15/85), 0.5 mL/min, 20 °C, retention time was the same as that of (***R***,***R***)**-3b**. >99%ee.

5.1.23. (*S*)-3-(4-(Diethyl(4-((*R*)-2-hydroxy-3,3-dimethylbutoxy)-3-methylphenyl)silyl)-2-methylphenoxy)propane-1,2-diol ((*R*,*S*)-3b′)

The title compound was prepared according to the procedure described for ((***R***,***R***)**-3b′**), starting from compound (***R***)**-11** and (*S*)-glycidol (4.5 mg, 19.9%). NMR spectra were the same as those of (***RS***,***S***)**-3b**. HRMS (FAB+): calcd for $C_{27}H_{43}O_5Si$ 475.2880, found 475.2902 ($M+H^+$). HPLC: Chiralpak IA (4.6 × 250 mm, IPA/hexane = 15/85), 0.5 mL/min, 20 °C, retention time was the same as that of (***R***,***S***)**-3b**. >99%ee.

5.1.24. (*S*)-(*R*)-1-(4-(Diethyl(3-methyl-4-(((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)phenyl)silyl)-2-methylphenoxy)-3,3-dimethylbutan-2-yl-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (12)

To a solution of (***R***)**-11** (9.5 mg, 0.024 mmol) in dichloromethane (0.2 mL) were added (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (0.0098 mL, 0.072 mmol) and pyridine (0.2 mL) at room temperature. The mixture was stirred at same temperature for 20 h and then evaporated, and the residue was purified by PTLC (hexane/ethyl acetate = 9/1) to give **12** (1.7 mg) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69–7.66 (m, 2H), 7.54 (d, 2H, J = 8.0 Hz), 7.47–7.44 (m, 3H), 7.33–7.31 (m, 3H), 7.28–7.21 (m, 4H), 7.04 (d, 1H, J = 8.5 Hz), 6.72 (d, 1H, J = 8.0 Hz), 5.34 (dd, 1H, J = 3.0, 7.5 Hz), 4.12 (dd, 1H, J = 3.0, 10. Hz), 4.05 (dd, 1H, J = 7.5, 10.5 Hz), 2.11 (s, 3H), 2.10 (s, 3H),1.03 (s, 9H), 1.03–0.96 (m, 10H). MS (FAB+) m/z: 833 ($M+H^+$).

5.1.25. (*R*)-(*R*)-1-(4-(diethyl(3-methyl-4-(((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)phenyl)silyl)-2-methylphenoxy)-3,3-dimethylbutan-2-yl-3,3,3-trifluoro-2-methoxy-2-Phenylpropanoate (13)

The title compound was prepared according to the procedure described for **12**, starting from compound (***R***)**-11** (9.5 mg) and (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (y. 2.6 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70–7.67 (m, 2H), 7.54 (d, 2H, J = 8.0 Hz), 7.45–7.44 (m, 3H), 7.34–7.32 (m, 2H), 7.26–7.21 (m, 3H), 7.12–7.09 (m, 3H), 7.05 (d, 1H, J = 8.5 Hz), 6.76 (d, 1H, J = 8.0 Hz), 5.40 (dd, 1H, J = 2.0, 8.0 Hz), 4.22 (dd, 1H, J = 2.0, 10. Hz), 4.15 (dd, 1H, J = 8.0, 10.0 Hz), 2.11 (s, 3H), 2.06 (s, 3H), 1.00 (s, 9H), 1.07–0.96 (m, 10H). MS (FAB+) m/z: 833 ($M+H^+$)

5.2. Reporter gene assays[34,35]

Human embryonic kidney (HEK 293) cells were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 5% fetal bovine serum (FBS) and antibiotic-antimycotic (Nacalai) at 37 °C in a humidified atmosphere of 5% CO_2 in air. Transfections were performed by the calcium phosphate coprecipitation method. Test compounds were added at 22 h after transfection. Cells were harvested approximately 16–20 h after the treatment, and luciferase and β-galactosidase activities were assayed using a luminometer and a microplate reader (ARVO-SX, Perkin Elmer, USA). In the DVR-reporter assay, DNA cotransfection experiments were done with 50 ng of reporter plasmid (TK-MH100x4-Luc), 10 ng of pCMX-s-galacosidase, and 15 ng of each receptor expression plasmid (CMX-GAL4 N-hVDR) per well in a 96-well plate. In the AR-reporter assay, DNA cotransfection experiments were done with 33 ng of reporter plasmid (ARE-tlc-Luc), 10 ng pCMX-s-galactosidase and 33 ng of each receptor expression plasmid (pSG5-hAR) per well in a 96-well plate. Luciferase data were normalized to an internal β-galactosidase control, and reported values are means of triplicate assays.

5.3. Androgen-antagonistic activity

Androgen-antagonistic activity of the compounds was evaluated by measurement of inhibition of androgen-induced SC-3 (Shionogi Carcinoma-3) cell growth, as described previously.[32,33] Briefly, SC-3 cells were cultured in Minimum Essential Medium, Alpha Modification (MEM-Alpha) supplemented with 2% FBS and 10 nM testosterone in the presence or absence of a test compound for three days at 37 °C under 5% CO_2. The number of cells with testosterone alone was defined as 100%. The concentration of test compounds that inhibited by 50% the increase of the cell number induced by 10 nM testosterone was quantified (IC_{50}) (Table 4). Androgen-agonistic activity can be evaluated in the same cell line,

but none of the prepared compounds showed androgen-agonistic activity (growth promotion of SC-3 cells).

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Supplementary data

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