Synthesis, Crystal Structure Analysis, and Pharmacological Characterization of Disila-bexarotene, a Disila-Analogue of the RXR-Selective Retinoid Agonist Bexarotene

Jürgen O. Daiss,[†] Christian Burschka,[†] John S. Mills,[‡] John G. Montana,[‡] Graham A. Showell,[‡] Ian Fleming,[§] Claudine Gaudon,[∥] Diana Ivanova,[∥] Hinrich Gronemeyer,[∥] and Reinhold Tacke*,[†]

Institut für Anorganische Chemie, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany, Paradigm Therapeutics Ltd., 162 Cambridge Science Park, Milton Road, Cambridge CB4 0GP, U.K., Department of Chemistry, Cambridge University, Lensfield Road, Cambridge CB2 1EW, U.K., and Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGMBC), CNRS/INSERM/ULP, BP 10142, F-67404 Illkirch Cedex, C. U. de Strasbourg, France

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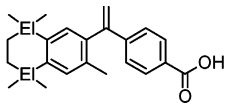
Twofold sila-substitution (C/Si exchange) in the saturated ring of the tetrahydronaphthalene skeleton of the RXR-selective retinoid agonist bexarotene (**1a**) leads to disila-bexarotene (**1b**). Compound **1b** was synthesized in a multistep synthesis, starting from 1,2-bis(chlorodimethylsilyl)ethane. The identity of **1b** was established by elemental analyses and multinuclear NMR studies, and the C/Si analogues **1a** and **1b** (and an intermediate in the synthesis of **1b**) were structurally characterized by single-crystal X-ray diffraction. Furthermore, **1a** and **1b** were studied for their interaction with retinoid X receptors. Although the twofold sila-substitution of **1a** resulted in significant differences in the molecular structures of **1a** and **1b**, disila-bexarotene (**1b**) was shown to be a highly potent RXR agonist.

Introduction

Bexarotene (Targretin, **1a**) is an RXR-selective retinoid that is in therapeutic use for treatment of cutaneous T-cell lymphoma.[1−4] In context with our systematic studies on sila-substituted drugs,[5,6] we were interested in the biological properties of the silicon analogue disila-bexarotene (**1b**). As almost all sila-analogues of drugs studied so far are antagonists,[5] the twofold sila-substitution of the retinoid agonist bexarotene was particularly challenging.



El = C: Bexarotene (**1a**)
El = Si: Disila-bexarotene (**1b**)

The molecular events by which RXR and other members of the nuclear receptor family regulate transcription of cognate gene programs are, at least in principle, reasonably well understood.[7] The signaling cascade relies on a precisely orchestrated recruitment and dissociation of transcription factors and molecular machineries to target gene promoters, which is initiated upon ligand binding. Multiple transcription activation, protein interaction, and crystallographic studies have revealed structural features of nuclear receptor ligand binding domains that are generated upon binding of agonists, antagonists, mixed agonists/antagonists, or inverse agonists, demonstrating an unexpected potential to modulate nuclear receptor action by ligand design.[8]

* To whom correspondence should be addressed. Phone: +49-931-888-5250. Fax: +49-931-888-4609. E-mail: r.tacke@mail.uni-wuerzburg.de.
[†] Universität Würzburg.
[‡] Paradigm Therapeutics Ltd.
[§] Cambridge University.
[∥] IGBMC.

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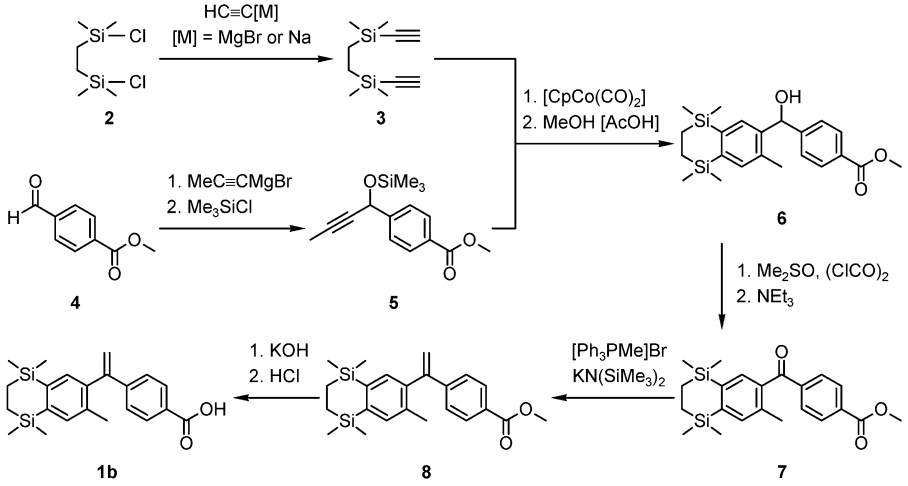
Scheme 1



Here we explore for the first time the activity of a ligand with a silicon-containing backbone.

Due to the different covalent radii of carbon and silicon, disila-substitution of the tetrahydronaphthalene skeleton of bexarotene was expected to change the conformation of the saturated ring and also to increase the lipophilicity (in this context, see ref 5). As carbon and silicon differ in their electronegativities, differences in the electronic properties (electrostatic potential) also have to be considered. All these changes could lead to different biological properties of the C/Si analogues **1a** and **1b**. We report here on (i) the synthesis of disila-bexarotene (**1b**), (ii) the crystal structure analyses of **1a** and **1b**, and (iii) the pharmacological characterization of **1a** and **1b** at retinoid X receptors. Preliminary results of these studies have been reported elsewhere.[9]

Results and Discussion

Synthesis. Disila-bexarotene (**1b**) was synthesized in a multistep synthesis, starting from 1,2-bis(chlorodimethylsilyl)ethane (**2**) (Scheme 1). Thus, treatment of **2** with ethynylmagnesium bromide gave 1,2-bis(ethynyldimethylsilyl)ethane (**3**; yield 80%). Alternatively, sodium acetylide instead of ethynylmagnesium bromide was used for this preparation (yield 71%). Treatment of methyl 4-formylbenzoate (**4**) with 1-propynylmagnesium bromide, followed by reaction with chlorotrimethylsilane, afforded methyl 4-[1-(trimethylsiloxy)but-2-ynyl]benzoate (**5**; yield 61%). Compounds **3** and **5** were then reacted in a cobalt-catalyzed [$CpCo(CO)_2$] Vollhardt cyclization,[10] followed by treatment with methanol in the presence of acetic acid, to give methyl 4-[hydroxy-(3,5,5,8,8-pentamethyl-5,8-disila-5,6,7,8-tetrahydro-2-naphthyl)methyl]benzoate (**6**; yield 22%). Oxidation of the alcohol **6** using Swern conditions (oxalyl chloride, dimethyl sulfoxide, triethylamine) afforded the corresponding ketone **7** (yield 87%), which was transformed into the corresponding olefin **8** using a Wittig-type

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Table 1. Crystal Data and Experimental Parameters for the Crystal Structure Analyses of 1a, 1b, and 8

	1a	1b	8
empirical formula	$C_{24}H_{28}O_2$	$C_{22}H_{28}O_2Si_2$	$C_{23}H_{30}O_2Si_2$
formula mass, g mol^{-1}	348.46	380.62	394.65
collecn T, K	173(2)	173(2)	173(2)
λ(Mo Kα), Å	0.710 73	0.710 73	0.710 73
cryst syst	triclinic	triclinic	monoclinic
space group (No.)	$P\bar{1}$ (2)	$P\bar{1}$ (2)	$P2_1/c$ (14)
a, Å	5.8732(12)	6.1056(10)	15.398(2)
b, Å	9.3259(19)	13.279(2)	24.713(4)
c, Å	18.156(4)	13.314(2)	5.9517(7)
α, deg	98.96(3)	97.06(2)	90
β, deg	94.03(3)	94.99(2)	95.485(16)
γ, deg	98.87(3)	95.04(2)	90
V, Å^3	966.0(3)	1061.9(3)	2254.5(5)
Z	2	2	4
D(calcd), g cm^{-3}	1.198	1.190	1.163
μ, mm^{-1}	0.074	0.180	0.172
F(000)	376	408	848
cryst dimens, mm	0.5 × 0.4 × 0.2	0.5 × 0.2 × 0.1	0.4 × 0.2 × 0.1
2θ range, deg	4.48−56.02	4.66−56.06	4.24−49.54
index ranges	$-7 \le h \le 7$	$-7 \le h \le 7$	$-18 \le h \le 18$
	$-12 \le k \le 12$	$-17 \le k \le 17$	$-29 \le k \le 28$
	$-23 \le l \le 23$	$-17 \le l \le 17$	$-6 \le l \le 6$
no. of collected rflns	12 700	13 959	11 326
no. of indep rflns	4306	4735	3822
R_{int}	0.0370	0.0406	0.0463
abs cor	none	numerical	none
max/min transmissn		0.9726/0.9108	
no. of rflns used	4306	4735	3822
no. of params	243	243	250
S^a	0.993	1.061	0.915
weight params a/b^b	0.0754/0.0000	0.0546/0.2327	0.0475/0.0000
$R1^c$ ($I > 2\sigma(I)$)	0.0407	0.0349	0.0342
$wR2^d$ (all data)	0.1152	0.0985	0.0831
max/min resid electron density, e Å^{-3}	+0.267/−0.193	+0.394/−0.272	+0.221/−0.143

[a] $S = \{\sum[w(F_o^2 - F_c^2)^2]/(n-p)\}^{0.5}$; n = no. of reflections; p = no. of parameters. [b] $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$, with $P = [\max(F_o^2,0) + 2F_c^2]/3$. [c] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. [d] $wR2 = \{\sum[w(F_o^2 - F_c^2)^2]/\sum[w(F_o^2)^2]\}^{0.5}$.

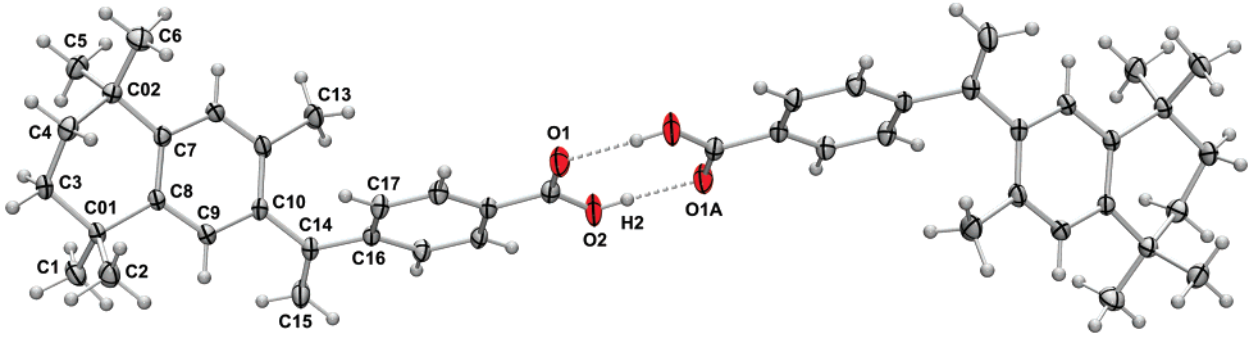

Figure 1. Centrosymmetric dimer in the crystal of **1a** (probability level of displacement ellipsoids 50%). Data for the hydrogen-bonding system (distances in Å and angles in deg):[11] O2−H2 = 0.89(2), H2···O1A = 1.772(19), O2···O1A = 2.6593(15); O2−H2···O1A = 176(2).

reaction (yield 90%). Treatment of **8** with potassium hydroxide in methanol/water and subsequent acidification with hydrochloric acid finally afforded the title compound **1b** (yield 96%).

Compounds **1b** and **6**−**8** were isolated as colorless crystalline solids, whereas **3** and **5** were obtained as colorless liquids. The identities of all these compounds were established by elemental analyses (C, H) and NMR studies (^{1}H, ^{13}C, ^{29}Si), and **1b** and **8** were additionally characterized by crystal structure analyses.

Crystal Structure Analyses. Compounds **1a**, **1b**, and **8** were structurally characterized by single-crystal X-ray diffraction. The crystal data and the experimental parameters used for these studies are given in Table 1. The molecular structures of **1a**, **1b**, and **8** are depicted in Figures 1−3; selected bond lengths, bond angles, and torsion angles are given in Table 2.[11]

The C/Si analogues **1a** and **1b** crystallize in the space group $P\bar{1}$. Both compounds form intermolecular O−H···O hydrogen bonds in the crystal, leading to the formation of centrosymmetric dimers (Figures 1 and 2). Compound **8** crystallizes in the space group $P2_1/c$.

As can be seen from Table 2, the conformations of the 5,8-disila-5,6,7,8-tetrahydronaphthalene skeletons of **1b** and **8** are very similar but differ significantly from the conformation of the 5,6,7,8-tetrahydronaphthalene moiety of **1a**. This is demonstrated in Figure 4 by the superposition of the respective partial structures of the C/Si analogues **1a** and **1b**. These differences result from the different covalent radii of carbon and silicon.

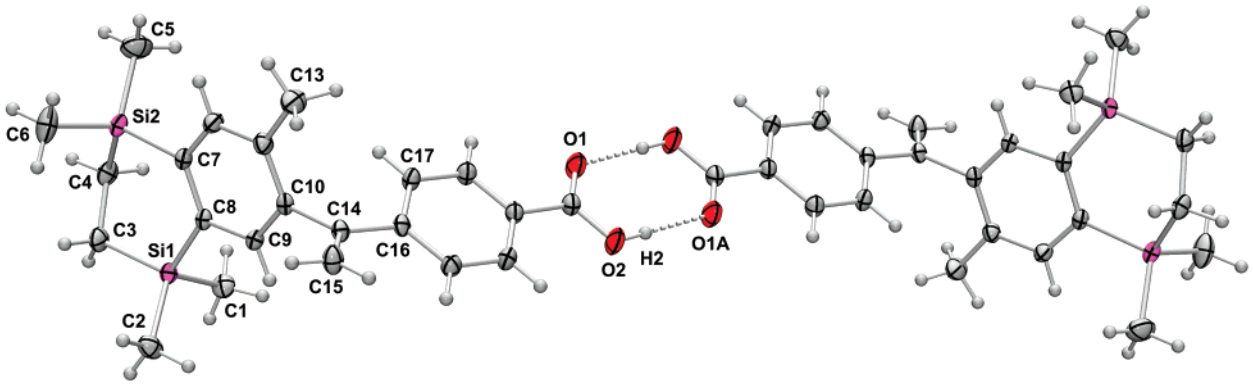

Figure 2. Centrosymmetric dimer in the crystal of **1b** (probability level of displacement ellipsoids 50%). Data for the hydrogen-bonding system (distances in Å and angles in deg):[11] O2−H2 = 0.83(2), H2···O1A = 1.83(2), O2···O1A = 2.6582(16); O2−H2···O1A = 174(2).

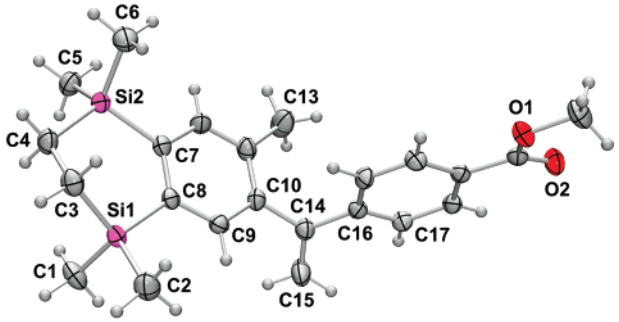

Figure 3. Molecular structure of **8** in the crystal (probability level of displacement ellipsoids 50%).

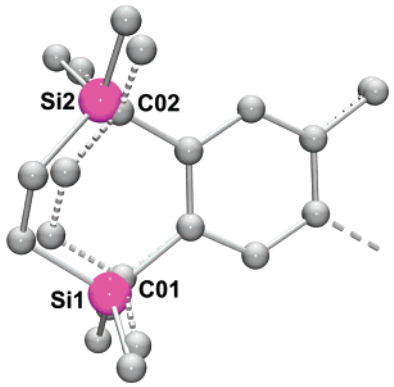

Figure 4. Superposition of the 3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl group of **1a** (dashed bonds) and the 5,8-disila-3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl group of **1b** (solid bonds). The hydrogen atoms are omitted for clarity.

Table 2. Selected Bond Lengths (Å), Bond Angles (deg), and Torsion Angles (deg) for 1a, 1b, and 8

	1a (El = C0)	**1b** (El = Si)	**8** (El = Si)
El1−C1	1.5331(18)	1.8665(15)	1.859(2)
El1−C2	1.5332(19)	1.8706(15)	1.869(2)
El1−C3	1.5407(16)	1.8735(14)	1.873(2)
El1−C8	1.5380(15)	1.8877(14)	1.8892(18)
El2−C4	1.5367(18)	1.8752(16)	1.875(2)
El2−C5	1.532(2)	1.8640(17)	1.864(2)
El2−C6	1.5347(18)	1.8711(17)	1.865(2)
El2−C7	1.5281(16)	1.8863(14)	1.8874(19)
C3−C4	1.5170(18)	1.548(2)	1.544(3)
C7−C8	1.4005(15)	1.4145(17)	1.411(3)
C1−El1−C2	109.05(10)	109.49(7)	108.77(11)
C1−El1−C3	107.85(10)	109.32(7)	110.82(10)
C1−El1−C8	109.18(10)	108.49(6)	107.96(9)
C2−El1−C3	109.28(11)	110.39(7)	108.86(11)
C2−El1−C8	110.27(10)	109.59(7)	112.67(9)
C3−El1−C8	111.16(9)	109.53(6)	107.77(9)
C4−El2−C5	111.44(10)	110.23(8)	108.27(9)
C4−El2−C6	107.28(12)	110.38(8)	112.11(11)
C4−El2−C7	108.79(9)	108.04(6)	110.28(9)
C5−El2−C6	108.38(11)	109.30(9)	109.38(11)
C5−El2−C7	109.37(11)	110.58(7)	109.70(9)
C6−El2−C7	111.60(10)	108.28(8)	107.07(9)
El1−C3−C4	112.70(10)	112.09(9)	111.66(15)
El1−C8−C7	123.39(10)	124.53(9)	121.27(13)
El2−C4−C3	111.57(11)	111.65(10)	114.03(13)
El2−C7−C8	122.67(10)	122.54(10)	125.11(13)
El1−C3−C4−El2	−64.15(15)	−65.85(12)	−61.61(18)
El1−C8−C7−El2	6.08(19)	1.09(16)	−5.2(2)
C3−El1−C8−C7	2.63(17)	−7.41(13)	−27.50(18)
C8−El1−C3−C4	−36.55(15)	42.37(13)	56.99(15)
C4−El2−C7−C8	18.69(16)	−18.21(13)	−5.3(2)
C7−El2−C4−C3	−52.40(14)	53.34(11)	35.26(19)
C9−C10−C14−C15	51.66(19)	−92.78(16)	62.3(3)
C9−C10−C14−C16	−126.74(13)	86.41(14)	−114.2(2)
C10−C14−C16−C17	26.45(17)	23.62(17)	−155.64(18)

As can be seen from Figures 1−3 and from the torsion angles listed in Table 2, the sp^2-hybridized carbon atoms C9, C10, C14, C15, C16, and C17 are not localized in one plane, probably due to the steric requirements of the C13-methyl group. The different torsion angles C9−C10−C14−C15, C9−C10−C14−C16, and C10−C14−C16−C17 of **1a**, **1b**, and **8** reflect the conformational flexibility of these compounds, which might be very important for receptor binding.

Pharmacological Studies. The RXR agonistic activity of disila-bexarotene at various concentrations was assessed and compared to that of bexarotene in a HeLa cell-based reporter assay. The cell line was engineered to express a chimeric receptor composed of the DNA binding domain of the GAL4 yeast transcription factor and the ligand binding domain of human RXRβ ("GAL4-RXRβ"). Additionally, this cell line harbors a stably integrated luciferase reporter that is under the control of five copies of the cognate GAL4 response element (referred to as "17mer") in front of a β-globin promoter ("17m × 5-βG-Luc"). Exposure of such reporter cells to rexinoid agonists activates luciferase production, which can be monitored by a luminometer or photon-counting camera. Furthermore, to sequester endogenous RAR and to prevent "false positive" signals due to signaling of a RAR retinoid via heterodimerization with the GAL4-hRXRβ, this cell line was also engineered to express a mutant form of RXR (mRXRαdnΔAB). The activity recorded in the cell line is, therefore, exclusively

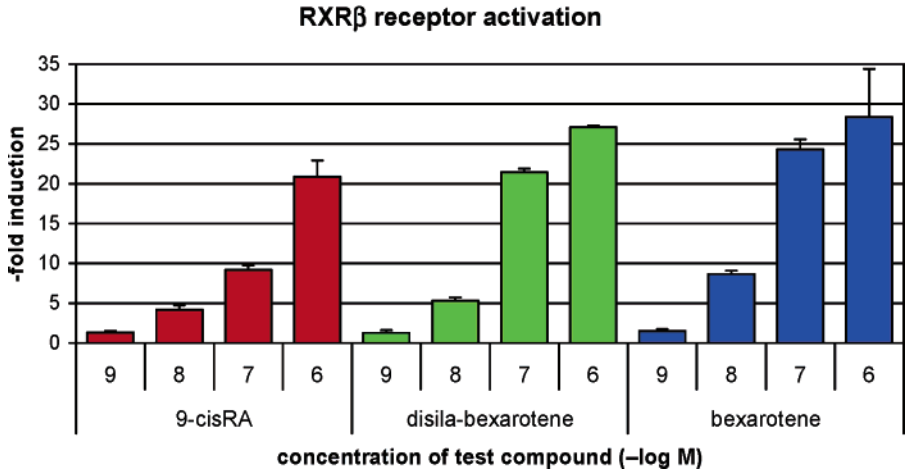

Figure 5. Agonistic activity of 9-*cis*-retinoic acid (9-cisRA), bexarotene (**1a**), and disila-bexarotene (**1b**). Data are means ±SEM of one experiment with at least three replicates.

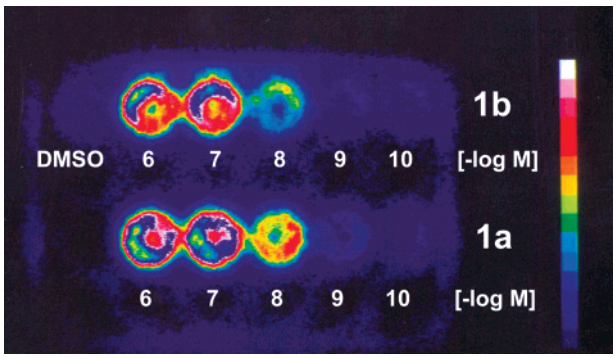

Figure 6. As demonstrated by a HeLa cell-based RXR reporter assay, disila-bexarotene (**1b**) is a highly potent RXR agonist. Cells engineered as described in the Experimental Section were exposed to 10^{-10}–10^{-6} M of **1a** or **1b** as indicated. The photo is a false-color representation of photons emitted from 160 000 reporter cells in each of the wells of a 24-well plate; exposure time was 3 min. DMSO is the vehicle control, indicating the background of the measurements.

mediated through RXR. The positive control is 9-*cis*-retinoic acid, and this natural ligand agonizes hRXRβ effectively, as shown by the clear dose response. Bexarotene is a more potent agonist than 9-*cis*-retinoic acid, and disila-bexarotene has a profile comparable to that of bexarotene (Figures 5 and 6), indicating that the disila-substitution of the tetrahydronaphthalene skeleton does not have a detrimental effect on the biological activity of bexarotene in terms of its ability to activate target genes through the RXR receptor. The silicon-induced molecular shape change and the likely changes in lipophilicity and electrostatic potential may, however, impact upon the pharmacodynamic profile of disila-bexarotene in vivo when compared to bexarotene. Further studies to investigate this aspect are in progress and will be reported elsewhere.

Experimental Section

Chemistry. General Procedures. All syntheses were carried out under dry nitrogen. The organic solvents used were dried and purified according to standard procedures and stored under dry nitrogen. Melting points were determined with a Büchi B-540 melting point apparatus using samples in open glass capillaries. The ^{1}H, ^{13}C, and ^{29}Si solution NMR spectra were recorded on a Bruker DRX-300 NMR spectrometer (^{1}H, 300.1 MHz; ^{13}C, 75.5 MHz; ^{29}Si, 59.6 MHz). CD_2Cl_2 or $CDCl_3$ was used as the solvent. All spectra were recorded at 22 °C. Chemical shifts were determined relative to internal $CHDCl_2$ (^{1}H, δ 5.32; CD_2Cl_2), CD_2Cl_2 (^{13}C, δ 53.8; CD_2Cl_2), $CHCl_3$ (^{1}H, δ 7.24; $CDCl_3$), $CDCl_3$ (^{13}C, δ 77.0; $CDCl_3$), or external TMS (^{29}Si, δ 0; CD_2Cl_2 or $CDCl_3$). Assignment of the ^{1}H NMR data was supported by ^{1}H,^{1}H gradient-selected COSY, ^{13}C,^{1}H gradient-selected HMQC and gradient-selected HMBC, and ^{29}Si,^{1}H gradient-selected HMQC (optimized for $^{2}J_{SiH}$ = 7 Hz), and assignment of the ^{13}C NMR data was supported by DEPT 135 and the aforementioned ^{13}C,^{1}H correlation experiments. The $^{2}J_{HH}$ coupling constants reported for the C=CH_2 groups represent absolute values.

4-[1-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)vinyl]benzoic Acid (Bexarotene; 1a). This compound was obtained using the methodology described in refs 1a,b.

Preparation of 4-[1-(3,5,5,8,8-Pentamethyl-5,8-disila-5,6,7,8-tetrahydro-2-naphthyl)vinyl]benzoic Acid (Disila-bexarotene; 1b). A mixture of methanol (120 mL), water (40 mL), potassium hydroxide (5.54 g, 98.7 mmol), and **8** (3.94 g, 9.98 mmol) was heated under reflux for 45 min (slow dissolution of **8**, quantitative conversion **8** → **1b** (HPLC)). The mixture was cooled in an ice bath, followed by addition of dichloromethane (100 mL), and the aqueous phase was acidified to ca. pH 1 by addition of 1 M hydrochloric acid (130 mL) (formation of a precipitate). The ice bath was removed, and the mixture was stirred at 20 °C for 5 min (dissolution of the precipitate). The organic phase was separated, the aqueous layer was extracted with dichloromethane (3 × 100 mL), and the organic extracts were combined and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was dried in vacuo (10 mbar, 20 °C, 1 h) to give 3.73 g of a white amorphous solid. This solid was dissolved in diethyl ether (85 mL), and **1b** was crystallized at 20 °C by vapor diffusion of *n*-pentane into this solution over a period of 2 weeks. The precipitate was isolated by decantation of the solvent, washed with *n*-pentane (2 × 20 mL), and dried in vacuo (0.001 mbar, 20 °C, 4 h) to give **1b** in 96% yield as a colorless crystalline solid (3.65 g, 9.59 mmol); mp 221 °C. ^{1}H NMR (CD_2Cl_2): δ 0.23 (s, 6 H, SiCH_3), 0.26 (s, 6 H, SiCH_3), 1.05 (s, 4 H, SiCH_2C), 2.00–2.02 (m, 3 H, CCH_3), 5.35 (d, $^{2}J_{HH}$ = 1.1 Hz, 1 H, C=CH_AH$_B$), 5.91 (d, $^{2}J_{HH}$ = 1.1 Hz, 1 H, C=CH$_A$$H_B$), 7.32–7.34 (m, 1 H, *H*-4, Naph (= 3,5,5,8,8-pentamethyl-5,8-disila-5,6,7,8-tetrahydro-2-naphthyl)), 7.35 (br s, 1 H, *H*-1, Naph), 7.37–7.43 (m, 2 H, *H*-3/*H*-5, Phe (= 1-carboxyphenyl)), 8.01–8.07 (m, 2 H, *H*-2/*H*-6, Phe), 11.4 (br s, 1 H, C(O)O*H*). ^{13}C NMR (CD_2Cl_2): δ −1.41 (2 C, SiCH_3), −1.39 (2 C, SiCH_3), 7.87 (SiCH_2C), 7.89 (SiCH_2C), 20.2 (CCH_3), 117.7 (C=CH_2), 127.0 (*C*-3/*C*-5, Phe), 128.5 (*C*-1, Phe), 130.6

(*C*-2/*C*-6, Phe), 135.2 (*C*-1, Naph), 135.7 (*C*-4, Naph), 136.0 (*C*-3, Naph), 141.0 (*C*-2, Naph), 143.3 (*C*-4a, Naph), 145.8 (*C*-8a, Naph), 146.5 (*C*-4, Phe), 149.3 (*C*=CH_2), 172.2 (*C*(O)OH). ^{29}Si NMR (CD_2Cl_2): δ −7.03, −6.98. Anal. Calcd for $C_{22}H_{28}O_2Si_2$: C, 69.42; H, 7.41. Found: C, 69.2; H, 7.4.

1,2-Bis(chlorodimethylsilyl)ethane (2). This compound was commercially available.

Preparation of 1,2-Bis(ethynyldimethylsilyl)ethane (3). Method A. This compound was synthesized according to ref 12.

Method B. A mixture of **2** (121 g, 562 mmol), sodium acetylide (300 g of an 18% suspension of NaC≡CH in xylene (mixture of isomers), 1.12 mol of NaC≡CH), and tetrahydrofuran (THF) (360 mL) was heated under reflux for 3 h. The mixture was cooled to 20 °C and washed with water (2 × 450 mL), and the organic layer was separated. The first aqueous wash solution (A) was extracted with diethyl ether (300 mL), the resulting ethereal extract was used to extract the second aqueous wash solution (B), and the organic extract was separated, followed by a second extraction of the wash solutions A and B with a fresh portion of diethyl ether (300 mL), using the same protocol as described for the first extraction sequence. All organic extracts were combined and dried over anhydrous sodium sulfate, most of the solvent was removed under reduced pressure, and the remaining xylene was then removed by vacuum distillation (30−50 °C/15 mbar) using a Vigreux column (40 cm). The residues from four identical runs of this preparation were combined and distilled in vacuo (Vigreux column, 40 cm) to give 245 g of pure (GC control) **3** (75−77 °C/20 mbar) and 126 g of a lower-boiling fraction containing **3** and xylene (50−75 °C/20 mbar). The latter fraction was redistilled (Vigreux column, 80 cm) to give a further 65 g of **3** (75−77 °C/20 mbar). Compound **3** was obtained in a total yield of 71% as a colorless liquid (310 g, 1.59 mol). ^{1}H NMR ($CDCl_3$): δ 0.16 (s, 12 H, SiC*H*$_3$), 0.60 (s, 4 H, SiC*H*$_2$C), 2.36 (s, 2 H, SiC≡C*H*). ^{13}C NMR ($CDCl_3$): δ −2.5 (Si*C*H$_3$), 8.1 (Si*C*H$_2$C), 89.1 (Si*C*≡CH), 93.6 (SiC≡*C*H). ^{29}Si NMR ($CDCl_3$): δ −12.8. Anal. Calcd for $C_{10}H_{18}Si_2$: C, 61.78; H, 9.33. Found: C, 61.6; H, 9.2.

Methyl 4-Formylbenzoate (4). This compound was commercially available.

Preparation of Methyl 4-[1-((Trimethylsilyl)oxy)but-2-ynyl]benzoate (5). A 0.5 M solution of 1-propynylmagnesium bromide in THF (422 mL, 211 mmol of MeC≡CMgBr) was added dropwise at −20 to −15 °C within 105 min to a stirred solution of **4** (34.6 g, 211 mmol) in THF (250 mL), and the mixture was then warmed to −10 °C within 2 h. Subsequently, chlorotrimethylsilane (27.5 g, 253 mmol) was added dropwise at −10 °C over a period of 30 min, and the mixture was warmed to 15 °C within 15 h. Most of the solvent was removed under reduced pressure at 5−15 °C, followed by addition of *n*-hexane (500 mL). The resulting precipitate was separated by filtration and washed with *n*-hexane (2 × 250 mL), and the organic solutions were combined. The solvent was removed under reduced pressure at 5−15 °C, and the residue was distilled in vacuo (Vigreux column, 10 cm) to give **5** in 61% yield as a colorless liquid (35.3 g, 128 mmol); bp 113 °C/0.0005 mbar. ^{1}H NMR (CD_2Cl_2): δ 0.20 (s, 9 H, SiC*H*$_3$), 1.87 (d, $^5J_{HH}$ = 2.2 Hz, 3 H, CC*H*$_3$), 3.89 (s, 3 H, C(O)OC*H*$_3$), 5.49 (q, $^5J_{HH}$ = 2.2 Hz, 1 H, SiOC*H*), 7.52−7.59 (m, 2 H, *H*-3/*H*-5, Phe′ (=1-(methoxycarbonyl)phenyl)), 7.97−8.04 (m, 2 H, *H*-2/*H*-6, Phe′). ^{13}C NMR (CD_2Cl_2): δ 0.2 (Si*C*H$_3$), 3.7 (C*C*H$_3$), 52.3 (O*C*H$_3$), 64.7 (SiO*C*H), 79.6 (*C*≡C), 83.1 (C≡*C*), 126.6 (*C*-3/*C*-5, Phe′), 129.9 (*C*-2/*C*-6, Phe′), 130.0 (*C*-1, Phe′), 147.6 (*C*-4, Phe′), 167.0 (*C*(O)OCH$_3$). ^{29}Si NMR (CD_2Cl_2): δ 20.5. Anal. Calcd for $C_{15}H_{20}O_3Si$: C, 65.18; H, 7.29. Found: C, 64.9; H, 7.2.

Preparation of Methyl 4-[Hydroxy-(3,5,5,8,8-pentamethyl-5,8-disila-5,6,7,8-tetrahydro-2-naphthyl)methyl]-benzoate (6). A solution of cyclopentadienylcobalt dicarbonyl ($CpCo(CO)_2$; 13.9 g, 77.2 mmol) in *m*-xylene (100 mL) was added dropwise within 16 h to a stirred boiling solution of **3** (149 g, 766 mmol) and **5** (212 g, 767 mmol) in *m*-xylene (1 L), followed (i) by addition of **3** (74.6 g, 384 mmol) in a single portion at 20 °C, (ii) then by dropwise addition of a solution of $CpCo(CO)_2$ (14.0 g, 77.8 mmol) in *m*-xylene (100 mL) within 11 h at reflux temperature, (iii) then by addition of **3** (74.5 g, 383 mmol) in a single portion at 20 °C, and (iv) finally by dropwise addition of a solution of $CpCo(CO)_2$ (14.0 g, 77.8 mmol) in *m*-xylene (100 mL) within 11 h at reflux temperature. (To avoid heating of the $CpCo(CO)_2$ solution before its addition, the dropping funnel containing this catalyst was separated from the refluxing reaction mixture by a glass tube (length, 20 cm), through which the $CpCo(CO)_2$ solution was allowed to drop freely into the refluxing mixture.) Most of the solvent (1 L) was removed by distillation at atmospheric pressure, methanol (1 L) and acetic acid (2.31 g, 38.5 mmol) were added, and the mixture was heated under reflux for 8 days. The mixture was cooled to 20 °C and then diluted with diethyl ether (1.5 L) and washed with a saturated aqueous sodium hydrogen carbonate solution (4 L). The organic layer was separated, the aqueous phase was extracted with diethyl ether (3 × 1 L), the organic solutions were combined and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The black tarry residue (982 g) was diluted with *n*-hexane/ethyl acetate (83/17 (v/v)) (1 L), followed by treatment with ultrasound at 20 °C for 1 h. The resulting mixture was divided into two equal portions, and each portion was purified by column chromatography on silica gel (column dimensions, 60 × 5 cm; silica gel (32−63 μm, ICN 02826), 600 g). The impurities (GC control) were eluted with *n*-hexane/ethyl acetate (83/17 (v/v)), and the product was eluted with *n*-hexane/ethyl acetate (80/20 (v/v)). The relevant fractions (GC control) of both chromatographic separations were combined, the solvent was removed under reduced pressure, and the residue was dried in vacuo (10 mbar, 20 °C, 1 h) to give 125 g of a brown solid, which was recrystallized twice from boiling *n*-heptane (6.25 L were used for each crystallization step; crystallization at 4 °C over a period of 1 day). The crystalline product was isolated by suction filtration, washed with cold (4 °C) *n*-heptane (600 mL), and dried in vacuo (0.001 mbar, 20 °C, 4 h) to give 54.2 g of **6**. The mother liquors, the wash solution, and the impure fractions (GC control) obtained from the chromatographic workup were combined, and the resulting solution was concentrated under reduced pressure and then dried in vacuo (0.001 mbar, 20 °C, 1 h) to give 112 g of a brown solid, which was purified by chromatography as described above. The resulting product (54.6 g) was recrystallized twice from *n*-heptane (2.73 L was used for each crystallization step) to give a further 12.4 g of **6**. Compound **6** was obtained in a total yield of 22% (related to **5**) as a colorless crystalline solid (66.6 g, 167 mmol); mp 166 °C. ^{1}H NMR (CD_2Cl_2): δ 0.17 (s, 3 H, SiC*H*$_3$), 0.22 (s, 9 H, SiC*H*$_3$), 1.01 (s, 4 H, SiC*H*$_2$C), 2.24 (br s, 3 H, CC*H*$_3$), 2.45 (d, $^3J_{HH}$ = 3.8 Hz, 1 H, O*H*), 3.87 (s, 3 H, C(O)OC*H*$_3$), 6.04 (d, $^3J_{HH}$ = 3.8 Hz, 1 H, OC*H*), 7.27 (br s, 1 H, *H*-4, Naph), 7.40−7.47 (m, 2 H, *H*-3/*H*-5, Phe′), 7.56 (br s, 1 H, *H*-1, Naph), 7.94−8.01 (m, 2 H, *H*-2/*H*-6, Phe′). ^{13}C NMR (CD_2Cl_2): δ −1.53 (Si*C*H$_3$), −1.46 (2 C, Si*C*H$_3$), −1.41 (Si*C*H$_3$), 7.78 (Si*C*H$_2$C), 7.83 (Si*C*H$_2$C), 19.5 (C*C*H$_3$), 52.3 (C(O)O*C*H$_3$), 73.7 (O*C*H), 127.1 (*C*-3/*C*-5, Phe′), 129.6 (*C*-1, Phe′), 129.9 (*C*-2/*C*-6, Phe′), 131.8 (*C*-1, Naph), 135.7 (*C*-3, Naph), 136.3 (*C*-4, Naph), 141.3 (*C*-2, Naph), 143.7 (*C*-4a or *C*-8a, Naph), 145.8 (*C*-4a or *C*-8a, Naph), 148.6 (*C*-4, Phe′), 167.1 (*C*(O)OCH$_3$). ^{29}Si NMR (CD_2Cl_2): δ −7.05, −6.95. Anal. Calcd for $C_{22}H_{30}O_3Si_2$: C, 66.28; H, 7.59. Found: C, 66.2; H, 7.6.

(11) The hydrogen-bonding system was analyzed by using the program system PLATON: Spek, A. L. PLATON; University of Utrecht, Utrecht, The Netherlands, 1998. In this context, see also: Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Structures*; Springer-Verlag: Berlin, Germany, 1991; pp 15−24.

(12) Kusumoto, T.; Hiyama, T. *Chem. Lett.* **1988**, 1149−1152.

Preparation of Methyl 4-[(3,5,5,8,8-Pentamethyl-5,8-disila-5,6,7,8-tetrahydro-2-naphthyl)carbonyl]benzoate (7). A solution of dimethyl sulfoxide (13.6 g, 174 mmol) in dichloromethane (55 mL) was added dropwise at −55 °C (±5 °C) within 60 min to a stirred solution of oxalyl chloride (11.0 g, 86.7 mmol) in dichloromethane (185 mL) (gas evolution), and the mixture was stirred for 15 min. Subsequently, a solution of **6** (31.5 g, 79.0 mmol) in dichloromethane (100 mL) was added dropwise at −55 °C (±5 °C) within 75 min, the mixture was stirred for 30 min, and triethylamine (40.0 g, 395 mmol) was added dropwise at the same temperature over a period of 30 min. (To avoid cooling of the solution of **6** before its addition, which would result in crystallization of **6** and incomplete conversion, the dropping funnel containing this solution was separated from the cold reaction mixture by a glass tube (length, 20 cm), through which the solution was allowed to drop freely into the cold mixture.) The mixture was stirred for a further 15 min at −55 °C and then warmed to 5 °C within 90 min (>97% conversion, GC control). The mixture was washed with water (2 × 400 mL), the organic phase was separated, the first aqueous wash solution (A) was extracted with diethyl ether (500 mL), the resulting ethereal extract was used to extract the second aqueous wash solution (B), and the organic extract was separated, followed by a second extraction of the wash solutions A and B with a fresh portion of diethyl ether (500 mL), using the same protocol as described for the first extraction sequence. The combined organic solutions were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was dried in vacuo (10 mbar, 20 °C, 1 h) to give a brown amorphous solid (30.3 g), which was purified by column chromatography on silica gel (column dimensions, 71 × 4 cm; silica gel (32−63 μm, ICN 02826), 480 g; eluent, *n*-hexane/ethyl acetate (87/13 (v/v)) to afford **7** as an amorphous colorless solid. The product was crystallized from boiling *n*-heptane (815 mL; crystallization at −20 °C over a period of 2 days), isolated by suction filtration, washed with cold (−20 °C) *n*-pentane (200 mL), and dried in vacuo (0.001 mbar, 20 °C, 6 h) to give 25.6 g of **7**. The mother liquor and the wash solution were combined, the resulting solution was concentrated under reduced pressure to a volume of 180 mL, and a further 1.7 g of the product was obtained by crystallization using the same method as described above. Compound **7** was obtained in a total yield of 87% as a colorless crystalline solid (27.3 g, 68.8 mmol); mp 118 °C. ^{1}H NMR (CD_2Cl_2): δ 0.17 (s, 6 H, SiCH_3), 0.28 (s, 6 H, SiCH_3), 1.05 (s, 4 H, SiCH_2C), 2.30−2.32 (m, 3 H, CCH_3), 3.93 (s, 3 H, C(O)OCH_3), 7.40 (s, 1 H, *H*-1, Naph), 7.43−7.46 (m, 1 H, *H*-4, Naph), 7.81−7.88 (m, 2 H, *H*-3/*H*-5, Phe′), 8.08−8.15 (m, 2 H, *H*-2/*H*-6, Phe′). ^{13}C NMR (CD_2Cl_2): δ −1.63 (2 C, SiCH$_3$), −1.59 (2 C, SiCH$_3$), 7.65 (SiCH$_2$C), 7.68 (SiCH$_2$C), 20.2 (CCH$_3$), 52.7 (C(O)OCH$_3$), 129.8 (*C*-2/*C*-6, Phe′), 130.3 (*C*-3/*C*-5, Phe′), 133.7 (*C*-1, Naph), 134.2 (*C*-1, Phe′), 136.46 (*C*-3, Naph), 136.49 (*C*-4, Naph), 137.9 (*C*-2, Naph), 141.7 (*C*-4, Phe′), 142.8 (*C*-4a, Naph), 149.8 (*C*-8a, Naph), 166.5 (*C*(O)OCH$_3$), 198.3 (C$_2$*C*=O). ^{29}Si NMR (CD_2Cl_2): δ −6.48, −6.42. Anal. Calcd for $C_{22}H_{28}O_3Si_2$: C, 66.62; H, 7.12. Found: C, 66.5; H, 7.0.

Preparation of Methyl 4-[1-(3,5,5,8,8-Pentamethyl-5,8-disila-5,6,7,8-tetrahydro-2-naphthyl)vinyl]benzoate (8). A 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene (29.7 mL, 14.9 mmol of KN(SiMe$_3$)$_2$) was added dropwise at 20 °C within 25 min to a stirred suspension of methyltriphenylphosphonium bromide (5.31 g, 14.9 mmol) in toluene (55 mL). The mixture was stirred at 20 °C for 45 min (initially, dissolution of [Ph$_3$PMe]Br; later, formation of a precipitate) and then added dropwise at 20 °C within 30 min to a solution of **7** (5.61 g, 14.1 mmol) in toluene (85 mL). The resulting mixture was stirred at 20 °C for a further 45 min and then added to a stirred mixture of a saturated aqueous solution of ammonium chloride (200 mL) (= solution A) and diethyl ether (150 mL), and the organic phase was separated and washed with water (200 mL) (= solution B). The first aqueous wash solution A was extracted with diethyl ether (150 mL), the resulting ethereal extract was used to extract the second aqueous wash solution B, and the organic extract was separated, followed by a second extraction of the wash solutions A and B with a fresh portion of diethyl ether (150 mL), using the same protocol as described for the first extraction sequence. All organic extracts were combined and dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure at 5−15 °C, and the solid colorless residue was dried in vacuo (0.001 mbar, 20 °C, 20 min). The crude product (11.1 g) was suspended in *n*-hexane/diethyl ether (70/30 (v/v)) (20 mL) and treated with ultrasound at 20 °C for 30 min (dissolution of **8** out of the nearly insoluble triphenylphosphine oxide). The resulting suspension was filtered over silica gel (32−63 μm, ICN 02826; column dimensions, 23 × 4 cm), which was washed with *n*-hexane/diethyl ether (70/30 (v/v)) (1 L). The filtrate and wash solution were combined (no residual Ph$_3$PO detected by GC), the solvent was removed under reduced pressure, and the residue was dried in vacuo (0.001 mbar, 20 °C, 1 h) to give a white amorphous solid (5.54 g), which was then crystallized from boiling *n*-hexane (165 mL; crystallization at −20 °C over a period of 3 days) to give **8** in 90% yield as a colorless crystalline solid (5.00 g, 12.7 mmol); mp 130 °C. ^{1}H NMR (CD_2Cl_2): δ 0.22 (s, 6 H, SiCH_3), 0.25 (s, 6 H, SiCH_3), 1.04 (s, 4 H, SiCH_2C), 1.98−2.00 (m, 3 H, CCH_3), 3.88 (s, 3 H, C(O)OCH_3), 5.31 (d, $^2J_{HH}$ = 1.2 Hz, 1 H, C=CH_AH$_B$), 5.87 (d, $^2J_{HH}$ = 1.2 Hz, 1 H, C=CH$_A$$H_B$), 7.30−7.38 (m, 4 H, *H*-3/*H*-5, Phe′, *H*-1/*H*-4, Naph), 7.92−7.97 (m, 2 H, *H*-2/*H*-6, Phe′). ^{13}C NMR (CD_2Cl_2): δ −1.42 (2 C, SiCH$_3$), −1.40 (2 C, SiCH$_3$), 7.86 (SiCH$_2$C), 7.89 (SiCH$_2$C), 20.2 (CCH$_3$), 52.3 (C(O)OCH$_3$), 117.2 (C=CH$_2$), 126.8 (*C*-3/*C*-5, Phe′), 129.6 (*C*-1, Phe′), 129.9 (*C*-2/*C*-6, Phe′), 135.1 (*C*-1, Naph), 135.7 (*C*-4, Naph), 136.0 (*C*-3, Naph), 141.1 (*C*-2, Naph), 143.3 (*C*-4a, Naph), 145.4 (*C*-4, Phe′), 145.7 (*C*-8a, Naph), 149.4 (*C*=CH$_2$), 167.0 (*C*(O)OCH$_3$). ^{29}Si NMR (CD_2Cl_2): δ −7.06, −7.01. Anal. Calcd for $C_{23}H_{30}O_2Si_2$: C, 70.00; H, 7.66. Found: C, 70.0; H, 7.6.

Crystal Structure Analyses. Suitable single crystals of **1b** and **8** were obtained directly from the preparation of these compounds (see above), whereas suitable single crystals of **1a** (mp 224−225 °C) were obtained by crystallization from a solution of **1a** (130 mg) in dichloromethane (5 mL) (slow evaporation of the solvent at 20 °C). The crystals were mounted in inert oil (perfluoroalkyl ether, ABCR) on a glass fiber and then transferred to the cold nitrogen gas stream of the diffractometer (Stoe IPDS; graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å)). The structures were solved by direct methods.[13] All non-hydrogen atoms were refined anisotropically.[14] The O*H* hydrogen atoms were localized in difference Fourier syntheses and refined freely. A riding model was employed in the refinement of the C*H* hydrogen atoms.

Assessment of Agonistic Activity of Bexarotene and Disila-bexarotene. Plasmids. All details about constructs are available upon request. Briefly, the (17m)$_5$-βglobin-Luc-Neo plasmid containing an expression cassette for the neomycin resistance gene was constructed by inserting a fragment derived from the 17m × 5-G-Luc construct[15] into pMAMneo-Luc (Clontech). A chimeric receptor expression construct encoding the yeast GAL4 DNA binding domain fused to the ligand binding domains of hRXRβ and containing the puromycin resistance gene was obtained by PCR amplification of a BglII fragment encompassing amino acids 271−534 of human RXRβ and cloning into the unique BamHI site of a

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pG4MpolyII-puromycin vector. The dnRXRαΔAB-hygromycin construct was generated by cloning a PCR amplified XbaI-flanked cassette comprising the PGK promoter-hygromycin and a PGK polyA tail[16] into the XbaI site of dnRXRαΔAB.[17]

Cell Culture. Cell Lines. HeLa cells were routinely maintained in DMEM supplemented with 5% FCS. Ligand assays were performed in DMEM + 5% charcoal dextran treated fetal calf serum without phenol red.

Stable Cell Lines. A stable GAL4-hRXRβ cell line to facilitate assessment of agonistic activity at RXRβ was obtained with minor modifications as described previously.[15] Briefly, HeLa cells were cotransfected with 5 μg of GAL4-hRXRβ and 10 μg of $(17m)_5$-βglobin-Luc-Neo reporter gene per 10 cm Petri dish. To sequester endogenous RAR and to prevent "false positive" signals due to signaling of a RAR retinoid via heterodimerization with GAL4-hRXRβ, 2 μg of mRXRαdnΔAB containing the hygromycin resistance gene was also included in the transfection procedure. At 48 h post-transfection, the cell line was selected with Geneticin at 0.8 mg mL^{-1}, puromycin at 0.3 μg mL^{-1}, and hygromycin at 0.2 mg mL^{-1}. Clones which expressed retinoic acid inducible luciferase were selected as described;[15] clones with high and reproducible inducible expression were expanded and aliquots frozen at early passages.

Assessment of Agonistic Activity. To test the different ligands, identical aliquots (usually $(1-2) \times 10^5$ cells in a 24-well plate) of the GAL4-hRXRβ reporter cell line were seeded and exposed in parallel to the known agonist 9-*cis*-retinoic acid, the test compounds, and vehicle for 8−16 h. Cells were lysed in 100 μL of lysis buffer (25 mM Tris phosphate (pH 7.8), 2 mM EDTA, 1 mM DTT, 10% glycerol, and 1% Triton X-100). A 100 μL portion of luciferin buffer (20 mM Tris phosphate (pH 7.8), 1.07 mM $MgCl_2$, 2.67 mM $MgSO_4$, 0.1 mM EDTA, 33.3 mM DTT, 0.53 mM ATP, 0.47 mM luciferin, and 0.27 mM coenzyme A) were added prior to direct photon counting. Agonistic activity for each test compound is represented as *n*-fold induction of reporter gene (luciferase) activity, measured by direct photon counting, relative to the vehicle control.

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Supporting Information Available: Tables of atomic coordinates and equivalent isotropic displacement parameters, anisotropic displacement parameters, experimental details of the X-ray diffraction studies, and bond lengths and angles for **1a**, **1b**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org. In addition, crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-267542 (**1a**), CCDC-267543 (**1b**), and CCDC-267544 (**8**). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax, (+44)1223/336033; e-mail, deposit@ccdc.cam.ac.uk).

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