$\leq 2\vartheta \leq 140°$) and the five-point method, monitoring one standard reflection every 50. Only 1430 reflections with $I > 2\sigma(I)$ [$\sigma(I)$ based on counting statistics] were considered as observed and used in the analysis. Seven low order reflections (0,2,0/-1,2,0/1,0,1/-2,0,1/-1,1,1/1,-1,1/-1,-1,1) were discarded in the last cycle of refinement. Lorentz and polarization were applied but not absorption.

The structure was solved via direct methods and refined by full-matrix least squares[22] with anisotropic and isotropic thermal parameters for non-hydrogen and hydrogen atoms respectively. All the hydrogens were located from difference Fourier map; H(41), H(42), H(51), and H(52) were constrained to ride on C(4) and C(5), respectively, during the last cycle of refinement. Final $R = 0.0853$, $R_w = 0.0869$, $w = [(F)^2 + 0.062F^2]^{-1}$ for 1430 reflections. The figures were obtained by using ORTEP[23] and PLUTO[24] whereas geometric calculations were performed with the PARST program.[25] All the calculations were performed using CRYSRULER.[26]

Pharmacological Methods. Carrageenan-Induced Paw Edema. Ten or 20 female Wistar rats (200-250-g body weight) were used for each group. Hind paw volumes were measured using a water pletysmometer (Basile, Varese, Italy) according to the method described by Winter et al.[27] Then the compounds to be tested were administered intraperitoneally (ip) at a constant dose of 50 mg/kg, by using a solution in aqueous $NaHCO_3$ (pH 7.4) at a concentration of 10 mg/mL. Control rats received the same volume of the vehicle. Thirty minutes later, 0.05 mL of 1% solution of carrageenan (Sigma, St. Louis, MO) was subcutaneously injected into the plantar surface of the right hind paw. The increase in paw volume 4 h after the injection of the phlogistic agent was adopted as a measure of the effect, and results were expressed as a precent reduction of control edema. Compounds showing 50% or more of inhibition (**7q** and **3**) were further tested at 25 mg/kg following the procedure described above. Compounds showing 20-50% of inhibition (**7a**, **7d**, **7e**, 7m, and **7n**) were tested at 100 mg/kg; for compounds (**7d**, 7m, and **7n**) that showed no increase in activity at 100 mg/kg, a full dose-response curve starting from 25 mg/kg was also carried out. Approximate ID_{50}s were calculated by plotting the log of the dose of the compound versus inhibition of paw edema. Student's t test for grouped data was used for statistical evaluations. Differences were considered to be statistically significant when p was 0.05 or lower.

Acknowledgment. This work was supported in part by a grant from the Consiglio Nazionale delle Ricerche and the Ministero della Pubblica Istruzione.

Registry No. 1, 1553-60-2; **2**, 22131-79-9; **4a**, 127-06-0; **4b**, 80606-74-2; **4c**, 1192-28-5; **4d**, 49805-38-1; **4e**, 100-64-1; **4f**, 1188-63-2; **4g**, 1113-74-2; **4h**, 4576-48-1; **4i**, 80606-77-5; **4j**, 4500-12-3; **4k**, 49805-57-4; **4l**, 30950-35-7; 4m, 10341-75-0; **4n**, 23517-42-2; **4o**, 574-66-3; **4p**, 2157-52-0; **4q**, 622-31-1; **4r**, 622-32-2; **4s**, 620-03-1; **4t**, 38266-87-4; **5**, 140-88-5; **6a**, 119881-14-0; **6b**, 125803-04-5; **6c**, 119881-16-2; **6d**, 125803-05-6; **6e**, 119881-17-3; **6f**, 125803-06-7; **6g**, 103586-50-1; **6h**, 125803-07-8; **6i**, 125803-08-9; **6j**, 125803-09-0; **6k**, 125803-10-3; **6**, 125803-11-4; 6m, 103586-51-2; **6n**, 125803-12-5; **6o**, 125803-13-6; **6p**, 119881-19-5; **6q**, 103586-48-7; **6r**, 125803-14-7; **6s**, 125803-15-8; **6t**, 125803-16-9; **7a**, 103586-55-6; **7b**, 125803-17-0; **7c**, 103586-53-4; **7d**, 125803-18-1; **7e**, 103586-54-5; **7f**, 103586-56-7; **7g**, 103604-67-7; **7h**, 103586-57-8; **7i**, 125803-19-2; **7j**, 125803-20-5; **7k**, 125803-21-6; **7l**, 125803-22-7; 7m, 103586-52-3; **7n**, 125803-23-8; **7o**, 15985-45-2; **7p**, 103586-60-3; **7q**, 103586-49-8; **7r**, 103586-70-5; **7s**, 103586-62-5; 7t, 103586-69-2.

Supplementary Material Available: Table IV giving final atomic coordinates and isotropic B equivalent, Table V giving anisotropic and isotropic thermal parameters, and Table VII giving cartesian coordinates of compounds 1, **2**, and **7c** (3 pages); Table VI giving observed and calculated structure factor amplitudes (8 pages). Ordering information is given on any current masthead page.

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Retinobenzoic Acids. 5. Retinoidal Activities of Compounds Having a Trimethylsilyl or Trimethylgermyl Group(s) in Human Promyelocytic Leukemia Cells HL-60

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The retinoidal activities of trimethylsilyl or trimethylgermyl-containing retinobenzoic acids are discussed on the basis of differentiation-inducing activity on human promyelocytic leukemia cells HL-60. Compounds with a trimethylsilyl or trimethylgermyl group at the meta position of the generic formula **2** have more potent activities than the corresponding retinobenzoic acids with a *m-tert*-butyl group. Compounds having two *m*-trimethylsilyl or -trimethylgermyl groups also have strong activities, and (*E*)-4-[3-[3,5-bis(trimethylsilyl)phenyl]-3-oxo-1-propenyl]benzoic acid (**22**, Ch55S) and (*E*)-4-[3-[3,5-bis(trimethylgermyl)phenyl]-3-oxo-1-propenyl]benzoic acid (**35**, Ch55G) are more active than retinoic acid by 1 order of magnitude. However, in the para-substituted chalcone derivatives, the replacement of a *tert*-butyl group (**49**, Ch40) with a trimethylsilyl (**27**, Ch40S) or a trimethylgermyl (**30**, Ch40G) group caused the disappearance of the activity.

Retinoids are defined as "substances that elicit specific biological responses (that is, the specific activities of retinoic acid) through binding to the specific receptor(s)".[1,2] Retinobenzoic acids are "a series of benzoic acid derivatives with potent retinoidal activities".[3] They modulate the cellular differentiation and proliferation in many types of cells in cases where retinoic acid (**1**, Chart I) acts as a modulator.[2,4] Their mechanism of action seems to be the same as that of retinoic acid,[5,6] and they also bind to the

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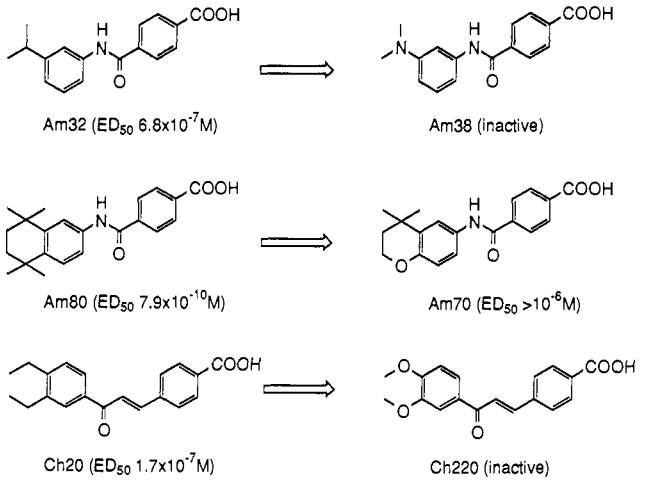
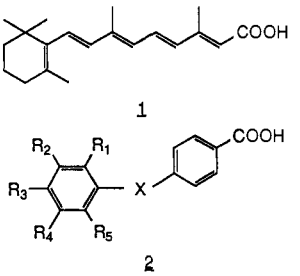


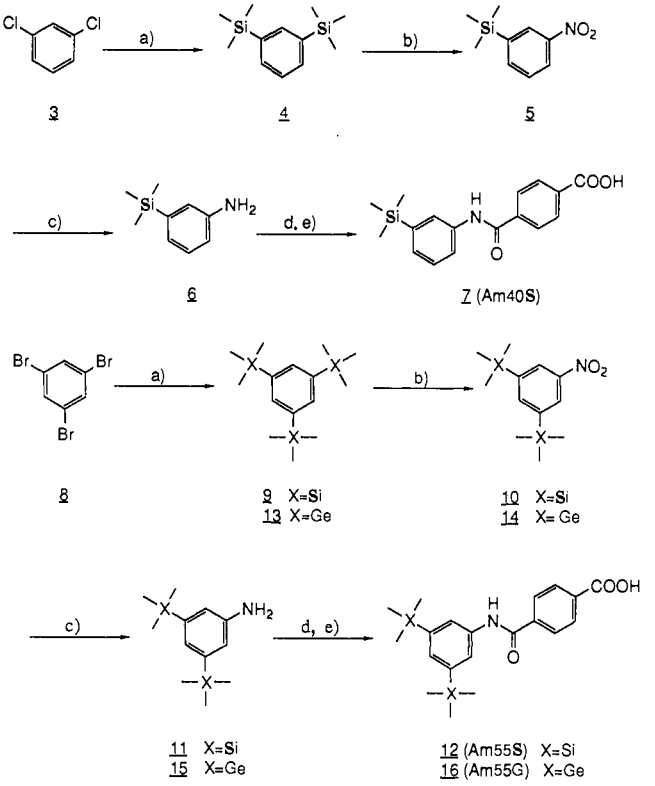
Figure 1. Diminished retinoidal activities caused by the introduction of polar atoms.

Chart I



same receptors.[7-9] The generic chemical structure of retinobenzoic acids is represented by **2**.[10] Groups necessary for retinoidal activities are a bulky alkyl group, such as an isopropyl or a *tert*-butyl group, at the meta (R_2) position on one benzene ring and a carboxyl group at the para position of the other benzene ring. The linking group X can be varied (such as -NHCO-,[11,12] -CONH-,[12,13] $-SO_2NH-$, -COCH=CH-)[14,15] -N=N-,[16,17] and so forth), regardless of the electronic properties. It has a role in locating the two essential groups, the *m*-alkyl group and the *p*-carboxyl group, at the proper positions.[18] Consequently, the orientation and the distance between the *m*-benzylic methyl group and the carboxyl group are the most important factors for the activity.[15,17,18] Contrary to the variability of the linking group X, the introduction of a polar atom, such as oxygen, sulfur, or nitrogen, into this alkyl group region causes remarkable diminution of the activity. Figure 1 shows that some compounds with a polar atom(s) instead of the benzylic carbon(s) have diminished abilities to induce differentiation of HL-60 cells.[12,15] Thus, the hydrophobicity in this region (R_2 and R_3) is an important factor for potent retinoidal activities. In view of these structure-activity relationships of retinobenzoic acids, we thought that it would be very interesting to examine the effect of replacement of the benzylic carbon with a silicon or germanium atom, members of the same group (group IVB) of the periodic table. These atoms are tetravalent and have some hydrophobicity, but have different electronic and steric properties from the carbon atom. Therefore, silyl or germyl substitution is expected to have an effect on activity or pharmacokinetic behavior. In this study, the retinoidal activities of some benzoic acid derivatives with a trimethylsilyl (TMS) or trimethylgermyl (TMG) group(s) are discussed, on the basis of the ability to induce differentiation of human promyelocytic leukemia cell line HL-60 to mature granulocytes.

Scheme I[a]



[a] (a) TMSCl (or TMGCl)/Mg; (b) fuming HNO_3/Ac_2O; (c) H_2/10% Pd-C; (d) *p*-$ClCOC_6H_4COOCH_3$/pyridine/benzene; (e) aqueous NaOH/EtOH.

Chemistry

TMS- or TMG-substituted terephthalic monoanilides were synthesized as shown in Scheme I. Because nitration of (trimethylsilyl)benzene is known to result in a mixture of three regioisomers of nitro(trimethylsilyl)benzene and nitrobenzene, which is formed by ipso attack (nitrodesilylation),[19,20] the method of selective nitrodesilylation of

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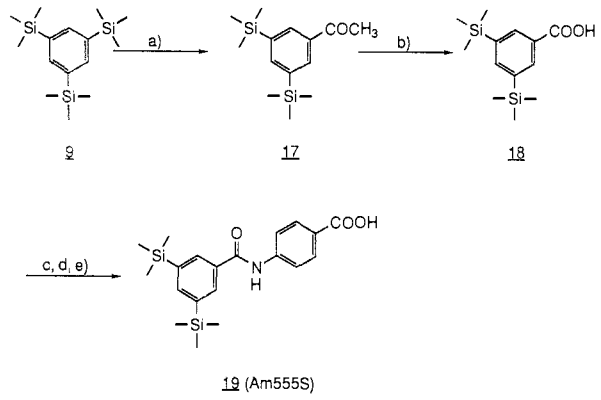
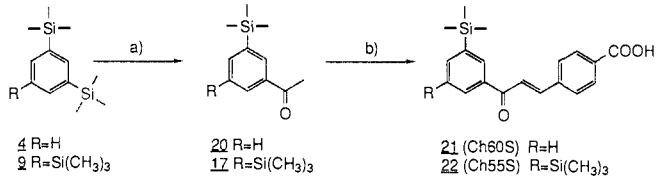
Scheme II[a]



[a] (a) $AcCl/AlCl_3/CS_2$; (b) $Ca(OCl)_2/K_2CO_3/KOH/H_2O$; (c) $SOCl_2$/benzene; (d) p-$NH_2C_6H_4COOCH_3/NEt_3$/benzene; (e) aqueous NaOH/EtOH.

Scheme III[a]



[a] (a) $AcCl/AlCl_3/CS_2$; (b) p-$HCOC_6H_4COOCH_3$/aqueous NaOH/THF.

poly-trimethylsilylated benzene was employed.[20,21] *m*-Bis(trimethylsilyl)benzene (**4**) was nitrated by fuming nitric acid in acetic anhydride to give *m*-nitro(trimethylsilyl)benzene (**5**) (50%). Similarly, *sym*-tris(trimethylsilyl)benzene (**9**) and *sym*-tris(trimethylgermyl)benzene (**13**) were nitrated to give 1-nitro-3,5-bis(trimethylsilyl)-benzene (**10**) (59%) and 1-nitro-3,5-bis(trimethylgermyl)benzene (**14**) (42%), respectively. These nitro compounds were hydrogenated and condensed with a terephthalic acid moiety to give **7** (Am40S), **12** (Am55S), and **16** (Am55G).

Anilide derivative **19** (Am555S), which possesses a reversed amide group compared with **12**, was synthesized by the acyldesilylation[19,20] (Scheme II). *sym*-Tris(trimethylsilyl)benzene (**9**) was acetylated by AcCl–$AlCl_3$ in CS_2 at 0 °C to give 3,5-bis(trimethylsilyl)acetophenone (**17**) (77%) and 3-(trimethylsilyl)acetophenone (**20**) (7%), which was formed by further protodesilylation. 3,5-Bis(trimethylsilyl)acetophenone (**17**) was converted to the corresponding substituted benzoic acid by the haloform reaction and then condensed with a *p*-aminobenzoic acid moiety to give **19**.

Chalcone-4-carboxylic acids with a TMS or TMG group(s) were prepared by two synthetic methods. One is the selective acyldesilylation described above (Scheme III). *m*-Bis(trimethylsilyl)benzene (**4**) was acetylated by AcCl–$AlCl_3$ in CS_2 at 0 °C to give 3-(trimethylsilyl)acetophenone (**20**) (44%) as a major product. 3-(Trimethylsilyl)acetophenone **20** was condensed with methyl terephthalaldehydate under basic aldol conditions to give **21** (Ch60S). Similarly, a bis(trimethylsilyl) derivative (**22**, Ch55S) was prepared by starting from *sym*-tris(trimethylsilyl)benzene (**9**). The other method for the synthesis of TMS or TMG-substituted acetophenones is tri-

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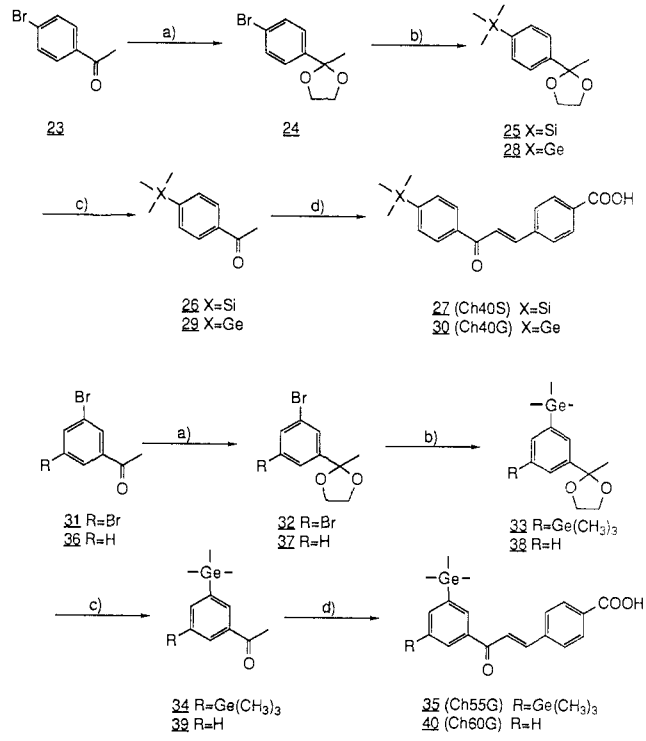
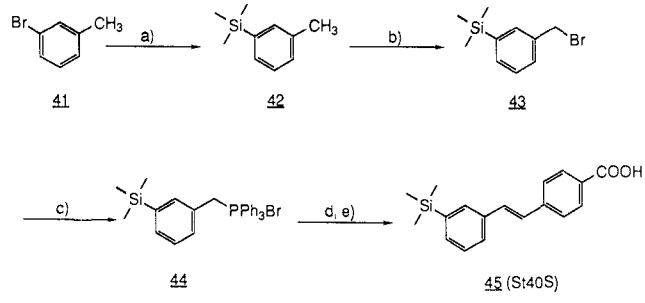
Scheme IV[a]



[a] (a) $HOCH_2CH_2OH/p$-TsOH/benzene; (b) TMSCl (or TMGCl)/Mg/THF; (c) pyridine·TsOH/acetone/H_2O; (d) p-$HCOC_6H_4COOCH_3$/aqueous KOH/THF (iPrOH).

Scheme V[a]



[a] (a) Li/ether; TMSCl; (b) NBS/AIBN/CH_2Cl_2; (c) PPh_3/toluene; (d) p-$HCOC_6H_4COOCH_3/NaOCH_3/CH_3OH$; (e) aqueous KOH/EtOH.

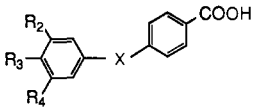
methylsilylation or trimethylgermylation of halogenated acetophenones whose carbonyl groups are protected (Scheme IV). *p*-Bromoacetophenone (**23**) was ketalized with ethylene glycol and then reacted with Mg and TMSCl to give 2-methyl-2-[4-(trimethylsilyl)phenyl]-1,3-dioxolane (**25**) (82%). Deprotection was carefully performed with pyridinium tosylate in quantitative yield. Deprotection using HCl/CH_3OH or $SiO_2 \cdot H_2O$ gave the protodesilylated compounds as byproducts. 4-(Trimethylsilyl)acetophenone (**26**) was condensed with methyl terephthalaldehydate under basic conditions to give **27** (Ch40S). Similarly, three corresponding TMG derivatives, **30** (Ch40G), **35** (Ch55G), and **40** (Ch60G), were synthesized from mono- or dibromoacetophenones (Scheme IV).

Stilbene-4-carboxylic acid (**45**, St40S) was synthesized from *m*-bromotoluene (**41**) by trimethylsilylation, followed by bromination, Wittig reaction with methyl terephthalaldehydate, and hydrolysis as shown in Scheme V.

Biological Results

The ability to induce differentiation of human promyelocytic leukemia cell line HL-60 to mature granulo-

Table I. Differentiation-Inducing Activity of Trimethylsilyl- or Trimethylgermyl-Containing Retinoids



compound (code name)	linking group X	substituent R_2	substituent R_3	substituent R_4	ED_{50}, M	relative activity[a]
1 (retinoic acid)					2.4×10^{-9}	100
7 (Am40S)	-NHCO-	TMS	H	H	8.5×10^{-8}	2.4
46 (Am40)		tBu	H	H	7.0×10^{-7}	0.32
12 (Am55S)		TMS	H	TMS	3.0×10^{-8}	13
16 (Am55G)		TMG	H	TMG	4.2×10^{-8}	15
47 (Am55)		tBu	H	tBu	3.6×10^{-8}	15
19 (Am555S)	-CONH-	TMS	H	TMS	9.2×10^{-9}	52.7
48 (Am555)		tBu	H	tBu	4.8×10^{-8}	5.6
27 (Ch40S)	-COCH=CH-	H	TMS	H	inactive at 10^{-6}	
30 (Ch40G)		H	TMG	H	inactive at 10^{-6}	
49 (Ch40)		H	tBu	H	2.8×10^{-8}	3.9
21 (Ch60S)		TMS	H	H	4.4×10^{-8}	1.8
40 (Ch60G)		TMG	H	H	4.0×10^{-8}	4.5
51 (Ch60)		tBu	H	H	1.6×10^{-7}	0.81
22 (Ch55S)		TMS	H	TMS	1.4×10^{-10}	860
35 (Ch55G)		TMG	H	TMG	2.1×10^{-10}	1000
50 (Ch55)		tBu	H	tBu	2.1×10^{-10}	640
45 (St40S)	-CH=CH-	TMS	H	H	1.0×10^{-9}	85
52 (St40)		tBu	H	H	1.0×10^{-8}	13

[a] Relative activity was defined as the ratio of ED_{50} (retinoic acid) to ED_{50} (a test compound), both values having been obtained in concurrent experiments, multiplied by 100. Therefore, this is not the simple ratio of the ED_{50} values shown in the table. The values shown are means of the ratios, when more than three repetitions were done, or representative ones (values for compounds 7 and 19).

cytes[22,23] was examined as a measure of retinoidal activity. This activity of retinoids correlates well with other retinoidal activities.[1] The morphological changes were examined after Wright-Giemsa staining, and the nitro blue tetrazolium (NBT) reduction assay was employed as a functional marker of differentiation.[24] These two indexes of differentiation correlated well.[11,13,14] Experiments were repeated at least twice, covering 5 magnitudes in concentration. The ED_{50} values of active compounds were calculated from the NBT reduction assay data. Relative activity was defined as the ratio of the ED_{50} of retinoic acid to the ED_{50} of a test compound, both values having been obtained *in concurrent experiments*. ED_{50} values and relative activities shown in Table I are representative ones or means.

The table shows the results of the differentiation-inducing activities of TMS or TMG-containing compounds, compared with the corresponding retinobenzoic acids having a *tert*-butyl (*t*Bu) group(s). Most of the silyl and germyl analogues of retinobenzoic acids have potent activities on HL-60 cells. Analogue **7**, the amide derivative with one *m*-TMS group, is more active than the corresponding *t*Bu derivative **46** by 1 order of magnitude. The introduction of the second *m*-*t*Bu group enhances the activity (**46** vs **47**). In the case of TMS-containing analogues, similarly, *m*,*m*-disubstituted compound **12** is more active than **7** and $^1/_7$ as active as retinoic acid. Analogue **16**, having two *m*-TMG groups, is also as active as the corresponding compounds **47** and **12**: There appears to be no different effect on activity with the three kinds of benzylic atom (C, Si, or Ge) in this series. In contrast, silyl analogue **19** has more potent differentiation-inducing activity than the corresponding carbon analogue **48**.

In the chalcone series, the derivatives with either one or two meta substituents have differentiation-inducing potencies. TMS-substituted compound **21** and TMG-substituted compound **40** are as active as or slightly more potent than the corresponding retinobenzoic acid with a *t*Bu group (**51**). However, the silyl or germyl analogue (**27** or **30**) is inactive below 10^{-6} M in the HL-60 assay, while *t*Bu congener **49** is active at 10^{-8} M (and more active than its meta isomer **51**). In the *t*Bu-containing chalcone series, para substitution is preferable, and this is exceptional throughout the structure–activity relationships for retinobenzoic acids.[17] In this case, also, the second meta substituent enhances activity. Thus, **22** and **35**, like **50** (Ch55), are more active than retinoic acid by approximately 1 order of magnitude.

Finally, 3′-(trimethylsilyl)stilbene-4-carboxylic acid (**45**) was found to be 6.5 times as active as **52**, which has a *m*-*t*Bu group. This result is similar to the case in the amide compounds (**7** vs **46**).

Discussion

A number of organosilicon derivatives of bioactive compounds have been synthesized and their activities have been investigated.[25] Such silyl-containing analogues could be classified roughly into two groups. One is silylated derivatives of known compounds, most of which are O- or N- (or occasionally C-) trimethylsilylated derivatives, useful mainly as prodrugs. The other group is organosilicon compounds having analogous structures to known bioactive carbon compounds, in which tetravalent silicon and germanium (though there are few examples of effective germanium analogues of drugs) are bioisosters of carbon.

In the monosubstituted retinobenzoic acids, generally, a TMS or TMG group at a meta position enhances activity more than a *t*Bu group. Thus, the low activities of **46** (Am40), **51** (Ch60), and **52** (St40) were increased by in-

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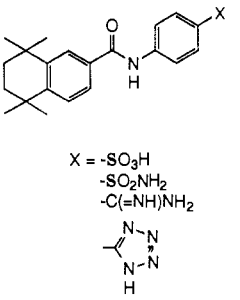
troduction of a silicon or germanium atom. In the case of the disubstituted compounds, the activities are nearly the same, regardless of the kind of benzylic atom. The only case where bis substitution (with TMS) led to an increase in activity over the carbon analogue was that involving **19** (Am555S) and 48 (Am555). Bis(trimethylsilyl) compound **22** (Ch55S) and bis(trimethylgermyl) compound **35** (Ch55G), which correspond to one of the most potent retinobenzoic acids, the di-*tert*-butyl compound **50** (Ch55), also have the highest activities and are more active than retinoic acid by 1 order of magnitude. In this case the introduction of silyl or germyl groups did not enhance the activity over that of the *t*Bu analogue, probably because the effective concentration of around 10^{-10} M is already so extremely low.

The increased activities may be partially due to the different chemical character of the silicon or germanium atom from that of the carbon atom. First, since the C–Si or C–Ge bond is longer than the C–C bond, the hydrophobic groups are sterically bulkier than the *t*Bu group. Thus, the volume of the hydrophobic region in the binding site of the receptor is somewhat larger than the volume of the *t*Bu group. This is also supported by the recent observation by Shroot et al. that some compounds possessing an adamantyl or 1-methylcyclohexyl group as the meta hydrophobic group of **2** had potent retinoidal activities.[26] Second, the silicon or germanium atom is more electropositive than the carbon atom. Therefore, the surface electronic potentials of the methyl groups attached to these atoms are more negative than those of the *t*Bu group or other groups of the compounds shown in Figure 1. It is an important finding that the significant benzylic carbon atom for the retinoidal activities or for the binding to the specific receptor can be replaced with a silicon or germanium atom.

The only exception was in the *para*-substituted chalcone derivatives, where the TMS (**27**, Ch40S) or TMG (**30** Ch40G) group failed to give differentiation-inducing activity, although **49** (Ch40) with a *p*-*t*Bu group conferred the activity. At present, we do not know whether this is due to the chemical characteristics resulting in a different affinity to the receptor from that of the carbon analogue or due to different pharmacokinetic–metabolic behavior.

Regarding the structure–activity relationships of retinobenzoic acids, the general formula (**2**) consists of three parts: hydrophobic alkylbenzene, the linking group X, and benzoic acid. From our previous studies,[12,15,17] the linking group X can be varied with retention of high and specific retinoidal activities, and so the chemical and physical properties of retinoids can vary widely. The result in this study showed that the carbon skeleton in the hydrophobic region is not essential and can be replaced with other hydrophobic groups. With respect to the last part of retinobenzoic acids, the benzoic acid moiety, or a functional group that can be a precursor of a carboxyl group (ester, amide, and other groups, which can be metabolized to the carboxylic acid), can be effective, although the activity is reduced by 1 or 2 orders of magnitude.[12,15] However, compounds which possess a sulfo, aminosulfonyl, amidino, or tetrazolyl group, instead of a carboxyl group (Chart II), are inactive or have very weak activity on HL-60 cells (data not shown). Such bioisosteric conversion of the terminal polar group was not successful, and so the carboxyl group (or groups metabolically convertible to the carboxylic acid) is the only essential group in the structure of retinobenzoic acids for the induction of differentiation of HL-60 cells.

Chart II



In conclusion, some trimethylsilyl or trimethylgermyl-containing benzoic acid derivatives are potent differentiation-inducers of HL-60 cells and should be included in the category of "retinoids". Since the physicochemical properties or pharmacological behavior of these compounds should be very different from those of conventional retinoids, they may be useful candidates for clinical applications as retinoids in oncology, dermatology, and immunology.

Experimental Section

Cells and Culture. The human promyelocytic leukemia cells HL-60 were provided by Prof. F. Takaku (Faculty of Medicine, University of Tokyo) and have been maintained in continuous suspension culture. The cells were cultured in plastic flasks in RPMI1640 medium, supplemented with 5% fetal calf serum (FCS) and antibiotics (penicillin G and streptomycin), at 37 °C in a humidified atmosphere of 5% CO_2 in air.

Test compounds were dissolved in ethanol at 0.2 mM and added to the cells, which were seeded at about 8×10^4 cells/mL; the final ethanol concentration was kept below 0.5%. Control cells were given only the same volume of ethanol. Retinoic acid, a positive control, was always assayed at the same time. The cells were incubated for 4 days and stained with Wright-Giemsa. Differential counts were then performed under a light microscope on a minimum of 200 cells. Nitro blue tetrazolium (NBT) reduction was assayed as described.[24] Cells were incubated for 20 min at 37 °C in RPMI1640 medium (5% FCS) and an equal volume of phosphate-buffered saline (PBS) containing NBT (0.2%) and 12-*O*-tetradecanoylphorbol-13-acetate (TPA; 200 ng/mL). The percentage of cells containing blue-black formazan was determined on a minimum of 200 cells. The results of these two evaluations were always in good agreement.

The assays of test compounds were performed at least twice. ED_{50} values of active compounds were calculated from the NBT reduction assay data by means of the van der Waerden method. Relative activities were calculated as the ratio of the ED_{50} of retinoic acid to the ED_{50} of the test compound obtained in concurrent experiments, multiplied by 100.

Chemistry. Melting points were determined by using a Yanagimoto hot-stage melting point apparatus and are uncorrected. Elemental analyses were carried out in the Microanalytical Laboratory, Faculty of Pharmaceutical Sciences, University of Tokyo, and were within ±0.4% of the theoretical values. NMR spectra were recorded on JEOL FX 100-MHz and JEOL GX 400-MHz NMR spectrometers. Chemical shifts are expressed in ppm relative to tetramethylsilane. Compounds with *tert*-butyl group(s) (compounds **46-52**) were prepared as described previously.[12,15,17]

4-[[3-(Trimethylsilyl)phenyl]carbamoyl]benzoic Acid (7, Am40S). A solution of *m*-dichlorobenzene (**3**, 15.0 g, 0.10 mol) in 30 mL of HMPA was added to a mixture of freshly distilled chlorotrimethylsilane (32.4 g, 0.30 mol) and Mg powder (6.0 g, 0.25 mol) in 60 mL of HMPA under Ar and the mixture was refluxed for 61 h.[27] The mixture was poured into ice water and was extracted with ether/*n*-hexane (2:1). The organic layer was washed with H_2O and brine and dried over Na_2SO_4. The crude

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mixture was distilled (bp_{3mmHg} 87–88 °C) to give *m*-bis(trimethylsilyl)benzene (**4**). A solution of 1.50 g (6.74 mmol) of **4** in 4 mL of Ac_2O was heated at 130 °C.[28] To this solution was added 1.6 mL of fuming nitric acid (94%; 36 mmol) in 5 mL of Ac_2O portionwise over 30 min, and stirring was continued for another 30 min. After cooling, the mixture was poured into ice-cooled 2% K_2CO_3 and extracted with CH_2Cl_2. The organic layer was washed successively with H_2O, 2% KOH (twice), H_2O, and brine and dried over Na_2SO_4. The crude mixture was chromatographed on silica gel to give *m*-nitro(trimethylsilyl)benzene (**5**, 50%), 1-nitro-2,4-bis(trimethylsilyl)benzene (15%), and 1,3-dinitro-5-trimethylsilylbenzene (2%). Compound **5** (200 mg, 1.02 mmol) was hydrogenated over 10% Pd–C (38 mg) in 7.5 mL of benzene.[21] The crude product was purified by silica gel column chromatography to give *m*-(trimethylsilyl)aniline (**6**, quant. yield). Compound **6** (135 mg, 0.87 mmol) was condensed with terephthalic acid monomethyl ester chloride (179 mg, 0.90 mmol) in 8 mL of dry benzene and 1 mL of pyridine. The mixture was poured into H_2O and extracted with AcOEt. The organic layer was washed successively with 0.2 M $Cu(NO_3)_2$, H_2O, 1 N $NaHCO_3$, H_2O, and brine and dried over Na_2SO_4. The crude mixture was chromatographed on silica gel to give methyl 4-[[3-(trimethylsilyl)phenyl]carbamoyl]benzoate (Am41S, quant. yield), which was hydrolyzed (aqueous NaOH–EtOH) to give **7** (Am40S, 61%). **Am41S**: colorless needles (from CH_2Cl_2–*n*-hexane); mp 125–126 °C; ^1H NMR (100 MHz, $CDCl_3$) δ 0.28 (s, 9 H), 3.96 (s, 3 H), 7.3–7.8 (m, 5 H), 7.93 (d, 2 H, J = 8 Hz), 8.13 (d, 2 H, J = 8 Hz); ^{13}C NMR (25 MHz, $CDCl_3$) δ −1.25 (q), 52.2 (q), 121.3 (d), 125.3 (d), 127.1 (d), 128.1 (d), 129.4 (d), 129.6 (d), 132.2 (s), 137.2 (s), 138.7 (s), 141.2 (s), 165.2 (s), 165.9 (s). **7 (Am40S)**: colorless prisms (from CH_3OH); mp 211–213 °C; ^1H NMR (100 MHz, $CDCl_3$–DMSO-d_6) δ 0.29 (s, 9 H), 7.3–7.8 (m, 4 H), 8.05 (d, 2 H, J = 8 Hz), 8.13 (d, 2 H, J = 8 Hz), 9.66 (br s, 1 H). Anal. ($C_{17}H_{19}NO_3Si\cdot{}^1/_4H_2O$) C, H, N.

4-[[3,5-Bis(trimethylsilyl)phenyl]carbamoyl]benzoic Acid (12, Am55S). A solution of *sym*-tribromobenzene (**8**, 12.5 g, 39.7 mmol) in 40 mL of THF was added slowly to a mixture of freshly distilled chlorotrimethylsilane (15.25 g, 140 mmol) and Mg powder (3.65 g, 150 mmol) in 15 mL of THF under Ar and the mixture was refluxed overnight. The mixture was filtered and the precipitate was washed with ether and CH_2Cl_2. The organic layer was washed with H_2O and dried over Na_2SO_4. The crude mixture was chromatographed on silica gel to give *sym*-tris(trimethylsilyl)benzene (**9**, 56%) and 3,3′,5,5′-tetrakis(trimethylsilyl)biphenyl (8%). A solution of 0.4 mL of fuming nitric acid (94%, 9.1 mmol) in 3 mL of Ac_2O was added to a solution of **9** (1.18 g, 4.00 mmol) in 2 mL of Ac_2O at −10 °C and the mixture was stirred for 2 h and then at room temperature overnight. The mixture was poured into ice-cooled 0.1 N NaOH and extracted with CH_2Cl_2. The organic layer was washed with H_2O and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel to give 1-nitro-3,5-bis(trimethylsilyl)benzene (**10**, 59%) and 2-nitro-1,3,5-tris(trimethylsilyl)benzene (16%). Compound **10** (264 mg, 0.99 mmol) was hydrogenated on 10% Pd–C (27 mg) in 15 mL of benzene. The crude product was purified by silica gel column chromatography to give 3,5-bis(trimethylsilyl)aniline (**11**, 96%). Compound **11** (220 mg, 0.93 mmol) was condensed with terephthalic acid monomethyl ester chloride (187 mg, 0.94 mmol) in 10 mL of dry benzene and 1 mL of pyridine. The mixture was poured into H_2O and extracted with AcOEt. The organic layer was washed successively with 0.2 M $Cu(NO_3)_2$, H_2O, 1 N $NaHCO_3$ and H_2O, and dried over Na_2SO_4. The crude product was recrystallized to give methyl 4-[[3,5-bis(trimethylsilyl)-phenyl]carbamoyl]benzoate (Am56S, 95%), which was hydrolyzed (aqueous NaOH–EtOH) to give **12** (Am55S, 88%). **Am56S**: colorless prisms (from CH_2Cl_2–*n*-hexane); mp 212.5–213.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.30 (s, 18 H), 3.97 (s, 3 H), 7.46 (t, 1 H, J = 1 Hz), 7.76 (d, 2 H, J = 1 Hz), 7.79 (br s, 1 H), 7.96 (d, 2 H, J = 8 Hz), 8.17 (d, 2 H, J = 8 Hz). **12 (Am55S)**: colorless needles (from AcOEt–*c*-hexane); mp 252–253.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.30 (s, 18 H), 7.46 (t, 1 H, J = 1 Hz), 7.77 (br s, 2 H), 7.80 (br s, 1 H), 7.99 (d, 2 H, J = 8 Hz), 8.21 (d, 2 H, J = 8 Hz). Anal. ($C_{20}H_{27}NO_3Si_2$) C, H, N.

4-[[3,5-Bis(trimethylgermyl)phenyl]carbamoyl]benzoic Acid (16, Am55G). Chlorotrimethylgermane (1.39 g, 9.07 mmol) and *sym*-tribromobenzene (**8**, 837 mg, 2.66 mmol) were added to a mixture of Mg (216 mg, 8.88 mmol) in 10 mL of THF under Ar and the mixture was refluxed for 5 h and then stirred at room temperature for 15 h. The mixture was diluted with petroleum ether and filtered. The precipitates was washed with petroleum ether and the filtrate was evaporated to give a pale-yellow oil. The crude mixture was chromatographed on silica gel and then distilled under vacuum (bp_{1mmHg} 90 °C) to give *sym*-tris(trimethylgermyl)benzene (**13**, 48%). A solution of 0.08 mL of fuming nitric acid (94%, 1.8 mmol) in 3 mL of Ac_2O was added to a solution of **13** (500 mg, 1.17 mmol) in 10 mL of Ac_2O at −10 °C and the mixture was stirred for 3 h. The mixture was poured into ice-cooled 1 N Na_2CO_3 and extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel to give 1-nitro-3,5-bis(trimethylgermyl)benzene (**14**, 42%). Compound **14** (125 mg, 0.35 mmol) was hydrogenated on 10% Pd–C (15 mg) in 10 mL of EtOH. The crude product was purified by silica gel column chromatography to give 3,5-bis-(trimethylgermyl)aniline (**15**, 94%). Compound **15** (108 mg, 0.33 mmol) was condensed with terephthalic acid monomethyl ester chloride (66 mg, 0.33 mmol) in 10 mL of dry benzene and 1 mL of pyridine. The mixture was poured into 2 N HCl and extracted with CH_2Cl_2. The organic layer was washed successively with H_2O, 0.2 M $Cu(NO_3)_2$, H_2O, and brine, and dried over Na_2SO_4. The crude product was chromatographed on silica gel to give methyl 4-[[3,5-bis(trimethylgermyl)phenyl]carbamoyl]benzoate (Am56G, 68%), which was hydrolyzed (aqueous NaOH–EtOH) to give **16** (Am55G, 82%). **Am56G**: colorless prisms; ^1H NMR (400 MHz, $CDCl_3$) δ 0.42 (s, 18 H), 3.97 (s, 3 H), 7.36 (t, 1 H, J = 1 Hz), 7.70 (br s, 2 H), 7.78 (br s, 1 H), 7.96 (d, 2 H, J = 8 Hz), 8.17 (d, 2 H, J = 8 Hz). **16 (Am55G)**: colorless prisms (from EtOH–*n*-hexane) mp 233–234 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.42 (s, 18 H), 7.35 (br s, 1 H), 7.75 (br s, 2 H), 7.97 (d, 2 H, J = 8 Hz), 8.16 (d, 2 H, J = 8 Hz). Anal. ($C_{20}H_{27}NO_3Ge_2$) C, H, N.

4-[[[3,5-Bis(trimethylsilyl)phenyl]carbonyl]amino]-benzoic Acid (19, Am555S). A solution of AcCl (130 mg, 1.66 mmol) in 5 mL of CS_2 (freshly distilled from P_2O_5) was added slowly to a mixture of *sym*-tris(trimethylsilyl)benzene (**9**, 500 mg, 1.70 mmol) and $AlCl_3$ (217 mg, 1.63 mmol) in 10 mL of CS_2 at 0 °C and the mixture was stirred for 1 h. After removal of the solvent, 1 N $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with H_2O and dried over $MgSO_4$. The crude mixture was chromatographed on silica gel to give 3,5-bis(trimethylsilyl)acetophenone (**17**, 77%), 3-(trimethylsilyl)acetophenone (**20**, 7%) and **9** (15%). A suspension of $Ca(OCl)_2$ (500 mg, 3.50 mmol), K_2CO_3 (345 mg, 2.50 mmol), and KOH (85%, 100 mg, 1.49 mmol) in 10 mL of H_2O was vigorously shaken at 65 °C for 30 min and then filtered.[29] Compound **17** (128 mg, 1.00 mmol) was added to the filtrate and the mixture was heated at 110 °C for 7.5 h. After cooling, $NaHSO_3$ (10 mg) was added and the mixture was extracted with AcOEt. The organic layer was washed with H_2O and brine and dried over Na_2SO_4. The crude mixture was chromatographed on silica gel to give 3,5-bis(trimethylsilyl)benzoic acid (**18**, 33%) and **17** (51%). A mixture of **18** (41 mg, 0.15 mmol), $CaCO_3$ (40 mg), $SOCl_2$ (40 mg, 0.34 mmol) and a drop of DMF in 5 mL of dry benzene was stirred at room temperature for 2 h. After filtration and removal of the solvent, the residue was dissolved in 5 mL of dry benzene. To this solution were added methyl 4-aminobenzoate (30 mg, 0.20 mmol) and 0.5 mL of triethylamine, and the mixture was stirred overnight. The mixture was poured into 0.5 N HCl and extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine and dried over Na_2SO_4. The crude mixture was chromatographed on silica gel to give methyl 4-[[3,5-bis(trimethylsilyl)phenyl]-carboxamido]benzoate (Am556S, 36%), which was hydrolyzed (aqueous NaOH–EtOH) to give **19** (Am555S, 66%). **19 (Am555S)**: colorless prisms (from AcOEt–*n*-hexane), mp 280 °C dec; ^1H NMR (400 MHz, $CDCl_3$) δ 0.33 (s, 18 H), 7.80 (d, 2 H, J = 8.5 Hz), 7.85 (br s, 1 H), 7.92 (br s, 1 H), 7.95 (br s, 2 H), 8.13 (d, 2 H, J = 8.5

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Hz). Anal. ($C_{20}H_{27}NO_3Si_2$) C, H, N.

(*E*)-4-[3-Oxo-3-[3-(trimethylsilyl)phenyl]-1-propenyl]benzoic Acid (21, Ch60S). A solution of AcCl (147 mg, 1.87 mmol) in 3 mL of CS_2 (freshly distilled from P_2O_5) was added slowly to a mixture of *m*-bis(trimethylsilyl)benzene (4, 419 mg, 1.88 mmol) and $AlCl_3$ (250 mg, 1.87 mmol) in 10 mL of CS_2 and the mixture was stirred for 5.5 h. After removal of the solvent, 1 N $NaHCO_3$ was added and the whole was extracted with CH_2Cl_2. The organic layer was washed with H_2O and dried over $MgSO_4$. The crude mixture was chromatographed on silica gel to give 3-(trimethylsilyl)acetophenone (**20**, 44%). To a solution of **20** (130 mg, 0.68 mmol) and methyl terephthalaldehydate (127 mg, 0.77 mmol) in 5 mL of THF was added 3 mL of 1 N NaOH and the mixture was stirred overnight. The mixture was poured into 0.5 N HCl and extracted with AcOEt. The organic layer was washed with H_2O and dried over Na_2SO_4. The crude mixture was chromatographed on silica gel to give **21** (30%). **21**: pale-yellow needles (from CH_2Cl_2–*n*-hexane); mp 179–180 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.33 (s, 9 H), 7.51 (t, 1 H, J = 8 Hz), 7.62 (d, 1 H, J = 16 Hz), 7.74 (d, 2 H, J = 8 Hz), 7.76 (d, 1 H, J = 8 Hz), 7.82 (d, 1 H, J = 16 Hz), 7.99 (d, 1 H, J = 8 Hz), 8.14 (d, 2 H, J = 8 Hz), 8.15 (m, 1 H). Anal. ($C_{19}H_{20}O_3Si$) C, H.

(*E*)-4-[3-[3,5-Bis(trimethylsilyl)phenyl]-3-oxo-1-propenyl]benzoic Acid (22, Ch55S). 3,5-Bis(trimethylsilyl)-acetophenone (**17**) and methyl terephthalaldehydate were condensed according to the method described for **21** to give **22** (66%). **22**: pale-yellow prisms (from AcOEt–*n*-hexane); mp 194–195.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.33 (s, 18 H), 7.59 (d, 1 H, J = 16 Hz), 7.73 (d, 2 H, J = 8 Hz), 7.80 (d, 1 H, J = 16 Hz), 7.87 (t, 1 H, J = 1 Hz), 8.10 (d, 2 H, J = 1 Hz), 8.16 (d, 2 H, J = 8 Hz). Anal. ($C_{22}H_{28}O_3Si_2$) C, H.

(*E*)-4-[3-Oxo-3-[4-(trimethylsilyl)phenyl]-1-propenyl]benzoic Acid (27, Ch40S). A mixture of 4-bromoacetophenone (**23**, 4.98 g, 25.0 mmol), ethylene glycol (2.33 g, 37.5 mmol), and *p*-TsOH·H_2O (238 mg, 1.25 mmol) in 180 mL of dry benzene was heated at reflux in a flask equipped with a Dean–Stark apparatus. After 8 h, ethylene glycol (1.55 g, 25 mmol) was added and the mixture was refluxed for 31 h. The mixture was washed with 1 N $NaHCO_3$, H_2O, and brine and dried over Na_2SO_4. 2-(4-Bromophenyl)-2-methyl-1,3-dioxolane (**24**) was obtained as colorless prisms (quant. yield). A mixture of Mg powder (250 mg, 10.3 mmol) and CH_3I (20 mg) was heated at reflux in 15 mL of freshly distilled THF under Ar for 1.5 h. A solution of **24** (2.11 g, 8.68 mmol) in 20 mL of THF was added and the mixture was heated at reflux for 1 h. Chlorotrimethylsilane (1.10 g, 10.1 mmol; freshly distilled) was added at 55 °C and the mixture was heated at reflux. After 4 h, chlorotrimethylsilane (0.30 g, 2.76 mmol) was added again, the refluxing was continued for 1.5 h, and then the mixture was stirred overnight at room temperature. The mixture was diluted with ether, washed with H_2O, 1 N HCl, and H_2O, and dried over Na_2SO_4. The crude product was chromatographed on silica gel to give 2-methyl-2-[4-(trimethylsilyl)phenyl]-1,3-dioxolane (**25**, 82%) as pale-yellow crystals (mp 59 °C). **25** (1.23 g, 5.20 mmol) and pyridinium tosylate (197 mg, 0.78 mmol) were dissolved in 30 mL of acetone and 4.7 mL of H_2O and the mixture was heated at reflux for 2.5 h and then stirred overnight at room temperature.[30] The solvent was removed and the residue was diluted with ether. The organic layer was washed successively with 1 N Na_2CO_3, H_2O, 0.2 M $CuSO_4$, and H_2O and dried over Na_2SO_4. The solvent was removed to give 4-(trimethylsilyl)-acetophenone (**26**, 99%) as a yellow oil. Compound **26** was condensed with methyl terephthalaldehydate according to the method described for **21** to give **27** (30%). **27**: pale-yellow prisms (from CH_3OH); mp 236.5–238.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.32 (s, 9 H), 7.61 (d, 1 H, J = 16 Hz), 7.68 (d, 2 H, J = 8 Hz), 7.73 (d, 2 H, J = 8 Hz), 7.82 (d, 1 H, J = 16 Hz), 7.99 (d, 2 H, J = 8 Hz), 8.14 (d, 2 H, J = 8 Hz). Anal. ($C_{19}H_{20}O_3Si$) C, H.

(*E*)-4-[3-Oxo-3-[4-(trimethylgermyl)phenyl]-1-propenyl]benzoic Acid (30, Ch40G). A solution of 2-(4-bromophenyl)-2-methyl-1,3-dioxolane (**24**, 972 mg, 4.00 mmol) in 12 mL of THF was added to a mixture of Mg turnings (108 mg, 4.44 mmol) and chlorotrimethylgermane (766 mg, 5.00 mmol), and the mixture was heated at reflux for 1.5 h and then stirred overnight at room temperature. The mixture was diluted with petroleum ether and filtered. The filtrate was evaporated and chromatographed on silica gel to give 2-methyl-2-[4-(trimethylgermyl)phenyl]-1,3-dioxolane (**28**, 83%) as colorless prisms (mp 63.5–65 °C). Compound **28** (420 mg, 1.50 mmol) and pyridinium tosylate (56 mg, 0.22 mmol) were dissolved in 10 mL of acetone and 1.35 mL of H_2O, and the mixture was heated at reflux for 2 h and then stirred overnight at room temperature. The mixture was poured into H_2O and extracted with petroleum ether. The organic layer was washed successively with 2 N HCl, H_2O, 1 N $NaHCO_3$, and H_2O and dried over Na_2SO_4. The crude product was chromatographed on silica gel to give 4-(trimethylgermyl)-acetophenone (**29**, 97%), which was condensed with methyl terephthalaldehydate in *i*PrOH according to the method described for **21** to give **30**. **30**: pale-yellow needles (from CH_3OH); mp 230–231 °C; ^1H NMR (400 MHz, $CDCl_3$), δ 0.44 (s, 9 H), 7.62 (d, 1 H, J = 16 Hz), 7.64 (d, 2 H, J = 8 Hz), 7.73 (d, 2 H, J = 8 Hz), 7.83 (d, 1 H, J = 16 Hz), 7.98 (d, 2 H, J = 8 Hz), 8.14 (d, 2 H, J = 8 Hz). Anal. ($C_{19}H_{20}O_3Ge$) C, H.

(*E*)-4-[3-[3,5-Bis(trimethylgermyl)phenyl]-3-oxo-1-propenyl]benzoic Acid (35, Ch55G). A mixture of 3,5-dibromoacetophenone[31] (**31**, 824 mg, 2.96 mmol), ethylene glycol (279 mg, 4.49 mmol), and *p*-TsOH·H_2O (29 mg, 0.15 mmol) in 100 mL of dry benzene was heated at reflux for 34 h in a flask equipped with a Dean-Stark apparatus. The mixture was washed with 1 N K_2CO_3 and H_2O and dried over Na_2SO_4. 2-(3,5-Dibromophenyl)-2-methyl-1,3-dioxolane (**32**) was obtained as colorless needles (76%, mp 74–74.5 °C). A solution of **32** (644 mg, 2.00 mmol) in 10 mL of THF was added to a mixture of Mg (108 mg, 4.44 mmol) and chlorotrimethylgermane (765 mg, 5.00 mmol) at 40 °C under Ar. The mixture was heated at reflux for 4.5 h and then stirred overnight at room temperature. The mixture was poured into ice–water and extracted with CH_2Cl_2. The organic layer was washed with H_2O and dried over Na_2SO_4. The crude product was chromatographed on silica gel to give 2-[3,5-bis-(trimethylgermyl)phenyl]-2-methyl-1,3-dioxolane (**33**, 70%). Compound **33** (240 mg, 0.60 mmol) and pyridinium tosylate (23 mg, 0.09 mmol) were dissolved in 10 mL of acetone and 0.54 mL of H_2O, and the mixture was heated at reflux for 2.5 h. The solvent was removed and the residue was diluted with ether. The organic layer was washed successively with H_2O, 1 N $NaHCO_3$, and H_2O and dried over Na_2SO_4. After the removal of the solvent, the crude product was purified by sublimation (0.5 mmHg, 70 °C) to give 3,5-bis(trimethylgermyl)acetophenone[32] (**34**, 89%) as colorless prisms (mp 56 °C). Compound **34** was condensed with methyl terephthalaldehydate in THF–*i*PrOH according to the method described for **21** to give **35** (54%). **35**: yellow prisms (from CH_2Cl_2–CH_3OH–*n*-hexane), mp 195.5 °C dec; ^1H NMR (400 MHz, $CDCl_3$) δ 0.45 (s, 18 H), 7.59 (d, 1 H, J = 16 Hz), 7.74 (d, 2 H, J = 8 Hz), 7.78 (t, 1 H, J = 1 Hz), 7.81 (d, 1 H, J = 16 Hz), 8.03 (d, 2 H, J = 1 Hz), 8.16 (d, 2 H, J = 8 Hz). Anal. ($C_{22}H_{28}O_3Ge_2$) C, H.

(*E*)-4-[3-Oxo-3-[3-(trimethylgermyl)phenyl]-1-propenyl]benzoic Acid (40, Ch60G). A mixture of 3-bromoacetophenone (**36**, 1.99 g, 10.0 mmol), ethylene glycol (931 mg, 15.0 mmol), and *p*-TsOH·H_2O (95 mg, 0.5 mmol) in 200 mL of dry benzene was heated at reflux in a flask equipped with a Dean–Stark apparatus for 4 days. After cooling, the mixture was washed with H_2O and dried over Na_2SO_4. The crude mixture was chromatographed on silica gel to give 2-(3-bromophenyl)-2-methyl-1,3-dioxolane (**37**, 83%). A solution of **37** (729 mg, 3.00 mmol) in 10 mL of THF was added to a mixture of Mg turnings (81 mg, 3.33 mmol) and chlorotrimethylgermane (574 mg, 3.75 mmol) at 40 °C under Ar. The mixture was heated at reflux for 4.5 h and then stirred overnight at room temperature. The mixture was diluted with petroleum ether and filtered. The filtrate was evaporated and the residue was chromatographed on silica gel to give 2-methyl-2-[3-(trimethylgermyl)phenyl]-1,3-dioxolane (**38**, 78%) as colorless cubes. Compound **38** (351 mg, 1.25 mmol) and pyridinium tosylate (47 mg, 0.19 mmol) were dissolved in 10 mL of acetone and 1.13 mL of H_2O, and the mixture was heated at reflux for 2.5 h. The solvent was removed and the residue was

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diluted with petroleum ether. The organic layer was washed successively with H_2O, 1 N $NaHCO_3$, and H_2O and dried over Na_2SO_4. The crude product was chromatographed on silica gel to give 3-(trimethylgermyl)acetophenone (**39**, 99%), which was condensed with methyl terephthalaldehydate in THF–*i*PrOH according to the method described for **21** to give **40** (22%). **40**: pale-yellow prisms (from AcOEt–*n*-hexane); mp 186–188 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.45 (s, 9 H), 7.50 (dd, 1 H, *J* = 7, 8 Hz), 7.62 (d, 1 H, *J* = 16 Hz), 7.72 (dt, 1 H, *J* = 1, 1, 7 Hz) 7.74 (d, 2 H, *J* = 8 Hz), 7.83 (d, 1 H, *J* = 16 Hz), 7.96 (ddd, 1 H, *J* = 1, 2, 8 Hz), 8.11 (m, 1 H), 8.14 (d, 2 H, *J* = 8 Hz). Anal. ($C_{19}H_{20}O_3Si \cdot {}^1/_4H_2O$) C, H.

(*E*)-4-[2-[3-(Trimethylsilyl)phenyl]ethenyl]benzoic Acid (45, St40S). A solution of *m*-bromotoluene (**41**, 7.7 g, 45 mmol) in 20 mL of dry ether was added slowly to 30% lithium dispersion in oil (2.32 g, 0.10 mol) in 10 mL of dry ether at −10 °C under Ar and the mixture was stirred for 3 h at room temperature. A solution of chlorotrimethylsilane (4.68 g, 43.1 mmol; freshly distilled from CaH_2) in 14 mL of dry ether was added, and the mixture was stirred for 36 h. After filtration, the filtrate was washed with H_2O and brine and dried over Na_2SO_4. The crude mixture was chromatographed on silica gel to give *m*-tolyltrimethylsilane (**42**, 54%). *N*-Bromosuccinimide (1.09 g, 6.12 mmol) and a catalytic amount of azobisisobutyronitrile were added to a solution of **42** (1.0 g, 6.09 mmol) in 6 mL of dry CH_2Cl_2 and the mixture was refluxed for 4.5 h. After cooling and filtration, the solvent was removed. The residue was chromatographed on silica gel to give 3-(trimethylsilyl)benzyl bromide (**43**, 70%). A mixture of **43** (730 mg, 3.00 mmol) and triphenylphosphine (1.18 g, 4.50 mmol) was refluxed in 10 mL of dry toluene under Ar for 4 h. [3-(Trimethylsilyl)benzyl]triphenylphosphonium bromide (**44**) was obtained by filtration (90%). Compound **44** (758 mg, 1.50 mmol) and methyl terephthalaldehydate (258 mg, 1.57 mmol) were added to a solution of Na (40 mg, 1.74 mmol) in 15 mL of dry methanol, and the mixture was stirred for 17 h. The precipitate was collected to give methyl (*E*)-4-[2-[3-(trimethylsilyl)phenyl]ethenyl]benzoate (St41S). The filtrate was chromatographed on silica gel to give St41S (total 70%) and its *Z* isomer (24%). St41S was hydrolyzed (aqueous KOH–EtOH) to give **45** (St40S, 85%). **St41S**: colorless needles (from CH_2Cl_2–*n*-hexane); mp 113–114.5 °C; ^1H NMR (100 MHz, $CDCl_3$) δ 0.30 (s, 9 H), 3.92 (s, 3 H), 7.0–7.6 (m, 8 H), 8.02 (d, 2 H, *J* = 8 Hz); UV λ_{max} (nm, log ε) 323 (4.91), 232 (4.61), 209 (4.75). **45 (St40S)**: colorless needles (from CH_2Cl_2–*n*-hexane); mp 216–218 °C; ^1H NMR (100 MHz, $CDCl_3$–DMSO-d_6) δ 0.30 (s, 9 H), 7.12 (d, 1 H, *J* = 18 Hz), 7.25 (d, 1 H, *J* = 18 Hz), 7.4–7.8 (m, 6 H), 7.95 (d, 2 H, *J* = 8 Hz). Anal. ($C_{18}H_{20}O_2Si \cdot {}^1/_4H_2O$) C, H.

Registry No. **3**, 541-73-1; **4**, 2060-89-1; **5**, 15290-24-1; **6**, 15290-25-2; **7**, 125973-48-0; **8**, 626-39-1; **9**, 5624-60-2; **10**, 78627-91-5; **11**, 125973-49-1; **12**, 125973-50-4; **13**, 125973-51-5; **14**, 125973-52-6; **15**, 125973-53-7; **16**, 125973-54-8; **17**, 81500-98-3; **18**, 125973-55-9; **19**, 125973-56-0; **20**, 17983-62-9; **21**, 125973-57-1; **22**, 125973-58-2; **23**, 99-90-1; **24**, 4360-68-3; **25**, 18192-28-4; **26**, 17983-61-8; **27**, 125973-59-3; **28**, 81805-70-1; **29**, 81805-71-2; **30**, 125973-60-6; **31**, 14401-73-1; **32**, 81500-93-8; **33**, 81500-96-1; **34**, 81500-99-4; **35**, 125973-61-7; **36**, 2142-63-4; **37**, 39172-32-2; **38**, 81805-70-1; **39**, 125973-62-8; **40**, 125973-63-9; **41**, 591-17-3; **42**, 3728-44-7; **43**, 17903-44-5; **44**, 125973-64-0; **45**, 125973-65-1; **46**, 102121-16-4; **47**, 116232-90-7; **48**, 104182-40-3; **49**, 119567-94-1; **50**, 110368-33-7; **51**, 119567-96-3; **52**, 102405-34-5; Am41S, 125973-66-2; Am56S, 125973-69-5; TMGCl, 1529-47-1; Am56G, 125973-70-8; Am556S, 125973-71-9; St41S (*E* isomer), 125973-72-0; St41S (*Z* isomer), 125973-73-1; *p*-$ClCOC_6H_4COOCH_3$, 7377-26-6; *p*-$NH_2C_6H_4COOH$, 619-45-4; *p*-$HCOC_6H_4COOCH_3$, 1571-08-0; 1-nitro-3,4-bis(trimethylsilyl)benzene, 78627-92-6; 1,3-dinitro-5-(trimethylsilyl)benzene, 125973-47-9; 3,3′,5,5′-tetrakis(trimethylsilyl)biphenyl, 125973-67-3; 2-nitro-1,3,5-tris(trimethylsilyl)benzene, 125973-68-4.

Synthesis and Pharmacological Evaluation of Amino, Azido, and Nitrogen Mustard Analogues of 10-Substituted Cannabidiol and 11- or 12-Substituted Δ^8-Tetrahydrocannabinol

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The synthesis of a variety of novel 10-substituted cannabidiol (CBD) and 11- or 12-substituted Δ^8-tetrahydrocannabinol (Δ^8-THC) analogues containing amino, alkylamino, azido, or a *N,N*-bis(2-chloroethyl)amino functional group is described, as well as their pharmacological evaluation in mice. These analogues, which possess only a portion of the full pharmacological spectrum of activity of Δ^9-THC, indicate that cannabinoid-mediated reduction of spontaneous locomotor activity, hypothermia, antinociception, and/or catalepsy need not be produced simultaneously, possibly suggesting the existence of more than one mechanism of action. The 10-substituted CBD analogues **3**, **4**, and **5** with an ethylamino, propylamino, or azido functional group, respectively, proved to be largely inactive, except for the production of central nervous system (CNS) depression concomitant with toxicity. Toxicity and CNS depression may be related phenomena in these nitrogenous compounds since 12-amino and 12-ethylamino analogues (**8** and **11**) of Δ^8-THC also proved to be very toxic. Antinociceptive and hypothermic responses (without reduction of motor activity) were observed at a dose of 10 mg/kg of the 11-ethylamino analogue (**9**) of Δ^8-THC, while a dose of 50 mg/kg of the nitrogen mustard 11-[*N,N*-bis(2-chloroethyl)amino]-Δ^8-THC (**12**) was necessary to produce any observable pharmacological effect. When selected analogues were evaluated for antagonistic properties, they failed to attenuate the effects of Δ^9-THC. Some nitrogen mustard analogues were capable of producing minimal pharmacological effects after either peripheral or direct CNS administration; however, these analogues also failed to attenuate the effects of Δ^9-THC either immediately after administration or 24–48 h later.

Δ^9-Tetrahydrocannabinol (Δ^9-THC) and certain analogues (e.g. Δ^8-THC) produce characteristic psychotropic responses in humans, as well as specific behavioral alterations in laboratory animals.[1] Other naturally occurring cannabinoids, such as cannabidiol (CBD, **1**), have been found to be devoid of many of these pharmacological effects, as well as devoid of psychoactive properties.[2] The pharmacological effects of the cannabinoids have been

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