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Preparation and biological activity of 13-substituted retinoic acids ☆

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Abstract—13-Demethyl or 13-substituted all-*E*- and 9*Z*-retinoic acids were synthesized using a palladium-catalyzed coupling reaction of enol triflates and tributylstannylolefins. Their biological activities were then measured. The 13-ethyl analogs exhibited approximately one-half of the antiproliferative and differentiation-inducing activity of ATRA in HL-60 cells. In contrast, in the 9*Z*-derivatives, all analogs, except for the 13-butyl derivatives, showed apoptosis-inducing activity.

1. Introduction

Retinoids are natural or synthetic analogs of retinoic acid. The all-*E*-retinoic acid (ATRA) **1a** and 9*Z*-retinoic acid (9CRA) **2a** are metabolites of vitamin A (retinol), which act as ligands for small molecular hormones that regulate gene transcription through the activation of retinoic acid receptors (RARα, β, and γ) and retinoid X receptors (RXRα, β, and γ).[2] The RARs and RXRs are members of a nuclear receptor superfamily and have several biological functions including cell differentiation, cell proliferation, and embryonic development.[3] The natural ligand all-*E*-retinoic acid binds with high affinity to RARs but does not bind to RXRs. In contrast, 9*Z*-retinoic acid has almost the same binding affinity toward both RXRs and RARs. Among their many biological functions, RXRs play an important role as heterodimers with other nuclear receptor proteins, including RARs, the thyroid-hormone receptor (TR), the vitamin-D receptor (VDR) and the peroxisome-proliferator-activated receptors (PPARs). Great efforts have been made to synthesize receptor-selective retinoids, not only to define the functions of specific receptors but also to develop therapeutic agents.[4] Following on from our study on the stereoselective synthesis of retinoids,[5,6] in order to clarify the structure–activity relationship of retinoids, we present a detailed description of the novel synthesis of 13-demethyl and 13-substituted all-*E*- and 9*Z*-retinoic acids, reported in a preliminary communication.[7]

2. Chemistry

β-Ionylideneacetaldehydes **3** are the main intermediates for the synthesis of retinoids, carotenoids and their stereoisomers. Our synthetic strategy is based on two coupling reactions of vinyl triflates (**A** and **D**) and vinyl stannanes (**B** and **C**).[8] The first coupling of segments **A** and **B** affords a stereoselective synthesis of β-ionylideneacetaldehydes. Segment **C**, which is used in the second coupling reaction, was derived from β-ionylideneacetaldehyde **3**, and segment **D** was obtained from ethyl acetoacetate (Scheme 1).

The vinyl triflate **5**,[6a] which was derived from the commercially available 2,6,6-trimethyl-1-cyclohexene-1-acetaldehyde **4**, was coupled with *E*- and *Z*-3-tributylstannyl-2-butenol,[9] **6** and **6′**, respectively, in the presence of 5 mol % of tris(dibenzylidene-acetone)dipalladium(0) ($Pd_2(dba)_3$) and triphenylarsine ($AsPh_3$) as a ligand[10,11] at room temperature in DMF to afford the alcohols **7**

Keywords: Coupling reaction; RAR; Retinoic-acid analogs; RXR.
☆ See Ref. 1.
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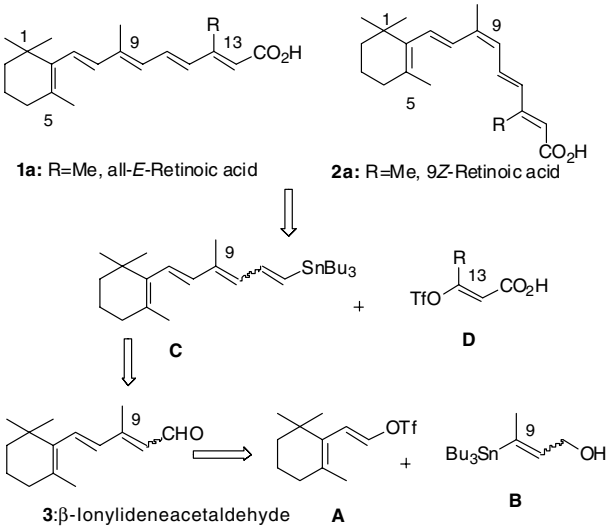
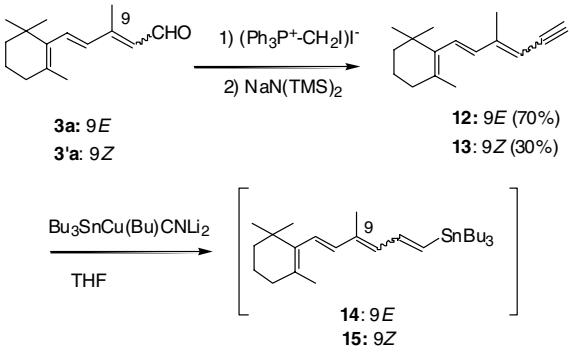


Scheme 1. Synthetic plan for 13-substituted retinoic acid.

and **8** in 76% and 87% yield, respectively. These alcohols were oxidized using MnO_2 to give the β-ionylideneacetaldehydes **3** and **3′** in 77% and 75% yield, respectively, without isomerization of the double bond. The all-*E*- and 9*Z*-13-demethylretinoic acids **1f** and **2f** were easily derived from β-ionylideneacetaldehydes **3** and **3′** by condensation with triethyl-phosphonocrotonate **9**, in which the *Z*-isomers of the connected position were not detected, followed by basic hydrolysis (Scheme 2).

Our attention then turned to the synthesis of 13-substituted retinoic acid analogs. 9*E*-β-Ionylideneacetaldehyde **3** was converted to the alkyne **12** using the Wittig reaction with (iodomethyl)triphenylphosphonium iodide, followed by elimination of hydrogen iodide using sodium bistrimethylsilylamide ($NaN(TMS)_2$) in 70% yield. Stannylcupration of **12** with lithium butyltributylstannylcyanocuprate prepared from CuCN and *n*-butyllithium[12] at −40 °C in tetrahydrofuran (THF) afforded the desired tetraenylstannane **14**, with excellent regio- and stereo-selectivities. As all attempts to isolate

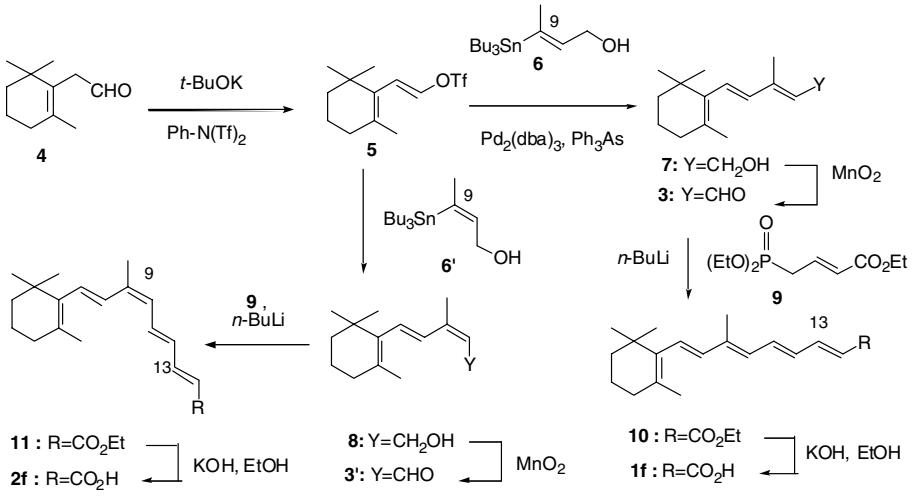


Scheme 3. Synthesis of segment **C**.

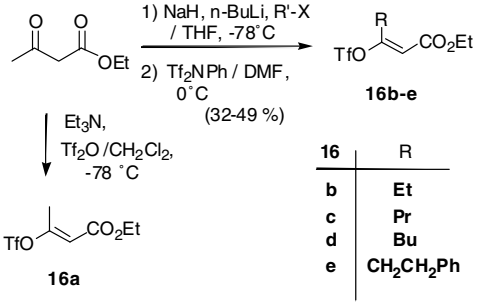
14 were unsuccessful, **14** was used in the next step without further purification, following the usual work-up. 9*Z*-Tetraenylstannane **15** was obtained from the 9*Z*-β-ionylideneacetaldehyde **3′** via the alkyne **13** using the method described above (Scheme 3).

Using the requisite segment **C**, we next investigated the preparation of segment **D**. It has been reported that the *E*- or *Z*-vinyl triflate from β-ketoester has been prepared stereoselectively by altering the solvent used in the reaction. Therefore, with THF as a solvent, the *Z*-triflate was obtained exclusively via a chelated intermediate formed from the enolated ketoester. However, using dimethylformamide (DMF) as a solvent, the chelated form was destroyed and *E*-triflate was obtained by quenching the thermodynamically stable *E*-enolate of the ketoester.[13] We prepared vinyl triflates (**16b–e**) in satisfactory yields using a one-pot procedure from the reaction of the alkylated intermediate of the dianion generated from ethyl acetoacetate with *N*-phenyl trifluoromethanesulfonimide (Tf_2NPh) in DMF solution (Scheme 4).

In order to optimize the coupling conditions, we tested the palladium-catalyzed coupling reaction of **14** with the *E*-vinyl triflate **16a**[14] in various solvents using 5 mol% of tris(dibenzylideneacetone)dipalladium(0)



Scheme 2. Synthesis of β-ionylideneacetaldehydes and 13-demethylretinoic acids.



Scheme 4. Synthesis of segment **D**.

Table 1. Cross-coupling of **14** with **16a** in several solvents[a]

Runs	Solvent	Reaction time (min)	Yield of **17a** (%)[b]
1	DMF	20	21
2	NMP	20	19
3	THF	60	22
4	DMF–THF (2:1)	30	60
5	NMP–THF (2:1)	30	41

[a] Conditions: solvent (6 mL), **14** (1 mmol), **16a** (1 mmol), $Pd_2(dba)_3$, (0.05 mmol), $AsPh_3$ (0.2 mmol) at room temperature.
[b] Yield in two steps.

Table 2. Yields of reactions for the synthesis of 13-substituted retinoic acids

Runs	Substituent R	Product	Yield (%)[a]	Product	Yield (%)
1	Me	**17a**	60	**1a**	83
2	Et	**17b**	65	**1b**	67
3	Pr	**17c**	66	**1c**	83
4	Bu	**17d**	44	**1d**	Quant.
5	$PhCH_2CH_2$	**17e**	65	**1e**	82
6	Me	**18a**	39	**2a**	Quant.
7	Et	**18b**	45	**2b**	Quant.
8	Pr	**18c**	48	**2c**	93
9	Bu	**18d**	58	**2d**	95
10	$PhCH_2CH_2$	**18e**	57	**2e**	91

[a] Yield in two steps.

($Pd_2(dba)_3$) and triphenylarsine ($AsPh_3$) as a ligand[10,11] at room temperature (Table 1). In the Stille coupling reaction between vinyl triflates and vinyl stannanes, polar solvents such as DMF or *N*-methylpyrrolidone (NMP) are known to significantly enhance the reaction rate and afford the coupling product in a relatively high yield.[10] However, in our study, the best result was obtained with a mixed solvent of DMF–THF (2:1), in which ethyl all-*E*-retinoate **17a** was obtained in a 60% yield (over two steps). The structure **17a** was determined by comparison of its spectral data with those reported in the literature,[5c] and the coupling reaction was found to proceed stereospecifically with retention of the double-bond configuration.

Similarly, other triflates **16b–e** coupled with *E*- or *Z*-tetraenylstannane **14** and **15** under optimized conditions to afford the corresponding esters **17** and **18** in moderate to good yields (two steps). Finally, these compounds were easily transformed into the corresponding retinoic acid analogs **1b–e** and **2b–e** in excellent yield by basic hydrolysis (Table 2; Scheme 5).

3. Biological evaluation

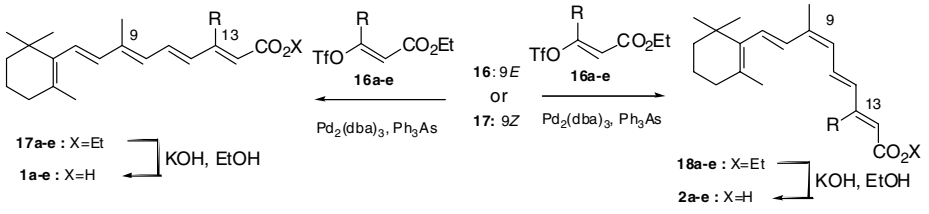
The retinoic acid analogs prepared as described above were initially tested for their antiproliferative, differentiation-inducing, and apoptosis-inducing activities in HL-60 cells. These results are summarized in Tables 3 and 4.

Compound **1b** showed approximately one-half of the antiproliferative activity of ATRA **1a**, and the demethyl analog **1f** exhibited one-tenth of the activity of ATRA. In analogs with side chains exceeding two carbon atoms, these activities were greatly decreased. Similarly, among the 9CRA analogs, **2b** exhibited approximately one-tenth of the activity of 9CRA **2a**, whereas the remaining analogs appeared to be inactive. This observation indicates that a methyl or ethyl group at the C-13 position in a retinoic acid is essential for antiproliferative activity. In the case of differentiation-inducing activity, similar trends were observed in both series of the ATRA and 9CRA analogs. None of the ATRA analogs exhibited apoptosis-inducing activity. However, all of the 9CRA analogs, with the exception of **2d**, induced apoptosis in HL-60 cells.

Table 3. Biological activity of the ATRA analogs

Compound	Antiproliferative activity	Differentiation-inducing activity	Apoptosis-inducing activity
1a (ATRA)	100	100	±
1f	11	11	–
1b	43	21	–
1c	1	6	–
1d	<0.3	<0.4	–
1e	6	2	–

The potency of the all-*E*-retinoic acid at ED_{50} was normalized to 100 in each case. +, positive; –, negative.
The ED_{50} of ATRA was 3.5×10^{-9} M for antiproliferative activity and 4.0×10^{-9} M for differentiation-inducing activity.



Scheme 5. Synthesis of 13-substituted retinoic acid.

Table 4. Biological activity of the 9CRA analogs

Compound	Antiproliferative activity	Differentiation-inducing activity	Apoptosis-inducing activity
2a (9CRA)	117	142	+
2f	2	1.4	+
2b	11	10	+
2c	1	<0.4	+
2d	<0.3	<0.4	−
2e	0.6	<0.4	+

The potency of the all-*E*-retinoic acid at ED_{50} was normalized to 100 in each case. +, positive; −, negative.
The ED_{50} of ATRA was 3.5×10^{-9} M for antiproliferative activity and 4.0×10^{-9} M for differentiation-inducing activity.

It is well documented that ATRA can induce the differentiation of HL-60 cells into monocytes or macrophages by binding to RARs, although it lacks the ability to induce apoptosis.[15] However, 9CRA can induce both HL-60 cell differentiation and apoptosis by binding to RARs and RXRs.[16] Our results were consistent with these previous findings. Therefore, the biological activities observed here are thought to result from the structure of the retinoid analogs bound to the specific retinoid (RARs and RXRs) receptors.

In order to determine whether the biological activity was mediated by retinoid receptors, the analogs were tested in an RXRα binding and transcriptional assay using a luciferase plasmid. The results are summarized in Figure 1. In the all-*E*-analogs, the binding affinity was similar to that of EtOH (blank). The remaining apoptotic activity of 9CRA analogs was explained by the fact that all except **2d** bind to RXRα with weak affinities compared to that of the native ligand (9CRA). Although an RAR-binding test was not performed, we suggest that the biological activity of the ATRA analogs prepared here reflects their binding affinities.

It can therefore be concluded that replacement of the methyl group at C-13 with a hydrogen, ethyl, propyl, or phenylethyl group greatly reduces the potency to regulate cell proliferation and differentiation, although the ability to induce apoptosis remains. Compounds **1d** and **2d**, which are the 13-butyl analogs of ATRA and 9CRA, respectively, were almost biologically inactive, probably as a result of the absence of binding affinity for RARs and RXRs. It is possible that the presence of a methyl or ethyl group at C-13 is essential for the expression of these activities in ATRA and 9CRA analogs.

In addition to the biological tests of antagonist and synergist activities, we also carried out binding studies using reporter plasmids containing RAR- and RXR-responsive DNA sequences. Furthermore, computer modeling of the interaction of the 13-substituent with the retinoid protein is currently in progress. The results of these studies will be published in the near future.

In summary, we have developed a novel method for the stereoselective synthesis of retinoid isomers using a new stereocontrolled formation of trisubstituted *E*- or *Z*-olefins by the modified Stille coupling reaction of alkenyl stannanes with vinyl triflates. This methodology could be applied to the synthesis of 13-substituted all-*E*- and 9*Z*-retinoic acids.[17] In addition, we have shown that a methyl group at C-13 in retinoic acid appears to be essential for the ATRA and 9CRA analogs to bind to RARs and RXRs, respectively.

4. Experimental

4.1. General methods

Ether refers to diethyl ether and hexane to *n*-hexane. *n*-BuLi was used as a solution in hexane. All melting points were determined using Yanagimoto micromelting point apparatus and uncorrected. UV–vis spectra were recorded on a JASCO Ubest-55 instrument in EtOH. IR spectra were recorded on a Perkin–Elmer FT-IR Paragon 1000 spectrometer in $CHCl_3$. ^1H NMR spectra at 300 or 500 MHz were measured on a Varian XL-300 or a Varian VXR-500 superconducting FT-NMR spectrometer with tetramethylsilane as an internal standard in deuteriochloroform. ^{13}C NMR spectra were recorded on a Varian VXR-500 instrument operating at 125 MHz in deuteriochloroform. Mass spectra were determined on a Hitachi M-4100 spectrometer. Column chromatography (CC) under reduced pressure was performed using Merck Silica gel 60. All reactions were carried out in a nitrogen atmosphere. THF and ether were purified by distillation from benzophenone–sodium ketyl under

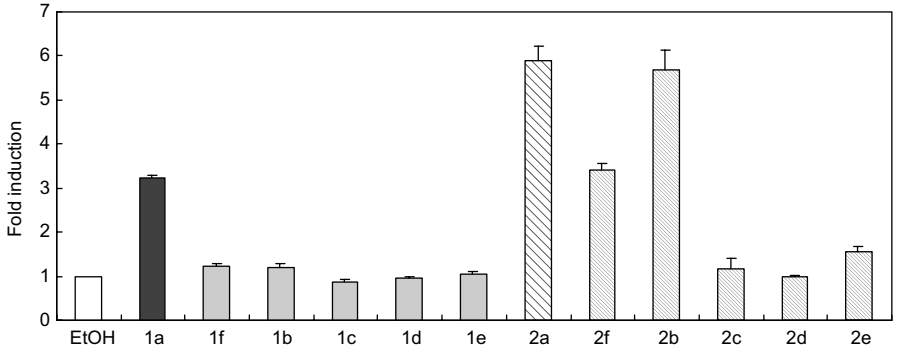


Figure 1. Transcriptional potency of ATRA, 9CRA, and its analogs on a human *RXRα-GAL4* expression gene in transfected MG-63 cells.

nitrogen. Other solvents used for reaction were dried prior to use. NaH was a 60% dispersion in mineral oil and used after washing with dry hexane. Other chemicals were of reagent grade and used without purification. Standard workup means that the organic layers were finally washed with brine, dried over anhydrous sodium sulfate (Na_2SO_4), filtered, and concentrated in vacuo below 30 °C using rotary evaporator.

4.1.1. (2*E*,4*E*)-3-Methyl-5-(2,6,6-trimethylcyclohexen-1-yl)-2,4-pentadienol (7). To a stirred solution of triflate[6a] (**5**, 900 mg, 3.0 mmol), triphenylarsin (152 mg, 0.5 mmol) and *E*-3-tributylstannyl-2-butenol (**6**, 1.64 g, 4.5 mmol, 1.5 equiv) in DMF (4 mL) was added $Pd_2(dba)_3{\cdot}CHCl_3$ (128 mg, 0.125 mmol) at room temperature under nitrogen. The resulting mixture was stirred for 2 h and the reaction was quenched with saturated aqueous NaCl (5 mL) and extracted with Et_2O (10 mL × 3), followed by the standard workup. The residue was purified by CC (ether–hexane = 3:7 as an eluent) to give the coupled alcohol (**7**, 500 mg, 76%) as a colorless oil.

IR ν_{max} cm^{-1}: 3610, 3450, 2959, 2928; ^1H NMR (300 MHz) δ: 1.01 (6H, s, Me), 1.3–1.7 (5H, m), 1.68 (3H, s), 1.85 (3H, s), 2.01 (2H, t, $J = 6.5$ Hz), 4.29 (2H, t, $J = 7$ Hz), 5.62 (1H, t, $J = 7$ Hz), 6.03 (1H, d, $J = 16.5$ Hz), 6.13 (1H, d, $J = 16.5$ Hz).

4.1.2. (2*Z*,4*E*)-3-Methyl-5-(2,6,6-trimethylcyclohexen-1-yl)-2,4-pentadienol (8). This compound was prepared from triflate (**5**, 730 mg, 2.5 mmol) and *Z*-3-tributylstannyl-2-butenol (**6′**, 1.19 g, 3.0 mmol) in the same manner as described for the preparation of **7** in 87% yield (478 mg).

IR ν_{max} cm^{-1}: 3607, 3440, 2960, 2930; ^1H NMR (300 MHz) δ: 1.01 (6H, s), 1.3–1.7 (5H, m), 1.70 (3H, s), 1.91 (3H, s), 2.02 (2H, t, $J = 6.5$ Hz), 4.31 (1H, t, $J = 7$ Hz), 5.54 (1H, t, $J = 7$ Hz), 6.18 (1H, d, $J = 16$ Hz), 6.38 (1H, d, $J = 16$ Hz).

4.1.3. (2*E*,4*E*)-3-Methyl-5-(2,6,6-trimethylcyclohexen-1-yl)-2,4-pentadienal (3). A mixture of alcohol (**7**, 400 mg, 1.8 mmol) and MnO_2 (4 g) in ether (20 mL) was stirred for 4 h. The reaction mixture was filtrated on Celite and the filtrate was concentrated in vacuo. The residue was purified by CC (ether–hexane = 1:4 as an eluent) to give the aldehyde (**3**, 302 mg, 77%). The spectral data of this compound was identical with those of the literature.[5c]

4.1.4. (2*Z*,4*E*)-3-Methyl-5-(2,6,6-trimethylcyclohexen-1-yl)-2,4-pentadienal (3′). This compound was prepared from the alcohol (**8**, 400 mg, 1.8 mmol) in the same manner as described for the preparation of **3** in 75% yield (294 mg). The spectral data of this compound was identical with those of the literature.[5c]

4.1.5. Ethyl all-*E*-13-demethylretinoate (10). To a stirred solution of triethyl 4-phosphonocrotonate (1.0 g, 4.0 mmol) and DMPU (4 mL, 20 mmol) in THF (10 mL) was added *n*-BuLi (1.59 M hexane solution, 2.52 mL, 4.0 mmol) at 0 °C. After stirring for 30 min, a solution was cooled at −78 °C and to this solution a solution of the aldehyde (**3**, 440 mg, 2.0 mmol) in THF (3 mL) was added. The resulting mixture was stirred for an additional 2 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with ether followed by standard workup. The residue was purified by CC (ether–hexane = 1:9 as an eluent) to give the pentaenyl ester (**10**, 365 mg, 58%) as a pale yellow solid.

Mp 85–87 °C (ether–hexane); UV λ_{max} nm: 261; IR ν_{max} cm^{-1}: 1697, 1621; ^1H NMR (300 MHz) δ: 1.02 (6H, s), 1.29 (3H, t, $J = 7$ Hz), 1.4–1.7 (4H, m), 1.70 (3H, s), 1.98 (3H, s), 2.03 (2H, t, $J = 6.5$ Hz), 4.19 (2H, q, $J = 7$ Hz), 5.85 (1H, d, $J = 15$ Hz), 6.11 (1H, d, $J = 12$ Hz), 6.13 (1H, d, $J = 15.5$ Hz), 6.29 (1H, d, $J = 15.5$ Hz), 6.32 (1H, dd, $J = 15$, 12 Hz), 6.94 (1H, dd, $J = 15$, 12 Hz), 7.38 (1H, dd, $J = 15$, 12 Hz); ^{13}C NMR (75 MHz) δ: 12.76, 14.28, 19.14, 21.67, 28.90 (2C), 33.05, 34.21, 39.54, 60.12, 119.77, 129.06, 129.29, 129.39, 130.18, 137.04, 137.14, 137.62, 137.64, 140.85, 167.23; HRMS (EI) m/z: Calcd for $C_{21}H_{30}O_2$ (M^+) 314.2244. Found: 314.2244.

4.1.6. Ethyl 9*Z*-13-demethylretinoate (11). This was prepared from the 9*Z*-aldehyde (**3′**, 440 mg, 2.0 mmol) and triethyl 4-phosphonocrotonate (1.0 g, 4.0 mmol) in the same manner as described for the preparation of **10** in 71% yield (450 mg) as a pale yellow oil.

UV λ_{max} nm: 256; IR ν_{max} cm^{-1}: 1697, 1620; ^1H NMR (300 MHz) δ: 1.03 (6H, s), 1.27 (3H, t, $J = 7$ Hz), 1.4–1.7 (4H, m), 1.74 (3H, s), 1.99 (3H, s), 2.03 (2H, t, $J = 6.5$ Hz), 4.19 (2H, q, $J = 7$ Hz), 5.84 (1H, d, $J = 15$ Hz), 6.03 (1H, d, $J = 12$ Hz), 6.26 (1H, d, $J = 16$ Hz), 6.29 (1H, dd, $J = 15$, 12 Hz), 6.64 (1H, d, $J = 16$ Hz), 7.03 (1H, dd, $J = 15$, 12 Hz), 7.36 (1H, dd, $J = 15$, 12 Hz); ^{13}C NMR (75 MHz) δ: 14.28, 19.13, 20.78, 21.76, 28.93 (2C), 33.04, 34.16, 39.49, 60.18, 119.77, 127.59, 128.60, 129.23, 130.38, 130.59, 136.01, 137.83, 139.50, 144.92, 167.22; HRMS (EI) m/z: Calcd for $C_{21}H_{30}O_2$ (M^+) 314.2244. Found: 314.2234.

4.1.7. all-*E*-13-Demethylretinoic acid (1f). A mixture of the ester (**10**, 124 mg, 0.4 mmol) and 10% KOH (3 mL) in EtOH (5 mL) was heated at 50 °C for 3 h. After cooling, the reaction mixture was made acidic by 5% HCl (7 mL) at 0 °C, and the organic was extracted with AcOEt (10 mL × 2), followed by a standard workup. the residue was purified by CC (ether–hexane = 3:7 as an eluent) to give the acid (**1f**, 86 mg, 77%), which was recrystallized from ether–hexane.

Mp 124–125.5 °C (ether–hexane); UV λ_{max} (ε) nm 344 (48,400); IR ν_{max} cm^{-1}: 3500–2600, 1679, 1618; ^1H NMR (300 MHz) δ: 1.03 (6H, s), 1.4–1.7 (4H, m), 1.72 (3H, s), 2.00 (3H, s), 2.03 (2H, t, $J = 6$ Hz), 5.86 (1H,

d, $J = 15$ Hz), 6.15 (1H, d, $J = 15$ Hz), 6.16 (1H, d, $J = 15$ Hz), 6.34 (1H, d, $J = 12$ Hz), 6.36 (1H, dd, $J = 15$, 12 Hz), 6.98 (1H, dd, $J = 15$, 12 Hz), 7.47 (1H, dd, $J = 15$, 12 Hz); ^{13}C NMR (75 MHz) δ: 14.28, 19.06, 21.71, 28.85 (2C), 33.31, 34.10, 39.49, 118.75, 128.67, 129.76, 131.81, 132.60, 135.31, 137.32, 139.23, 142.30, 146.97, 172.08; HRMS (EI) m/z: Calcd for $C_{19}H_{26}O_2$ (M^+) 286.1932. Found: 286.1936.

4.1.8. 9*Z*-13-Demethylretinoic acid (2f). This was prepared from the ester (**11**, 135 mg, 0.43 mmol) in the same manner as described for the preparation of **1f** in 73% yield (89 mg).

Mp 104–106 °C (ether–hexane); UV λ_{max} (ε) nm: 341 (31,000); IR ν_{max} cm^{-1}: 1697 (CO), 1620 (C=C); ^{1}H NMR (300 MHz) δ: 1.04 (6H, s), 1.4–1.7 (4H, m), 1.75 (3H, s), 2.01 (3H, s), 2.05 (2H, t, $J = 6$ Hz), 5.85 (1H, d, $J = 16$ Hz), 6.05 (1H, d, $J = 9.5$ Hz), 6.29 (1H, dd, $J = 15$, 9.5 Hz), 6.31 (1H, d, $J = 15$ Hz), 6.66 (1H, d, $J = 16$ Hz), 7.08 (1H, dd, $J = 15$, 12 Hz), 7.46 (1H, dd, $J = 15$, 12 Hz); ^{13}C NMR (75 MHz) δ: 15.17, 20.79, 22.58, 28.93 (2C), 31.52, 34.16, 36.09, 118.72, 127.49, 128.31, 129.13, 130.56, 130.95, 137.15, 137.80, 140.32, 147.23, 172.41; HRMS (EI) m/z: Calcd for $C_{19}H_{26}O_2$ (M^+) 286.1932. Found: 286.1929.

4.1.9. (3*E*,5*E*)-4-Methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3,5-hexadien-1-yne (12). To a stirred suspension of (Ph_3PCH_2I)I (2.12 g, 4.00 mmol) in THF (10 mL) was added a solution of NaN(TMS)$_2$ (4.0 mL, 1.0 M in THF, 4.0 mmol) at −78 °C. After stirring for an additional 20 min, to this mixture were added HMPA (1.2 mL, 7 mmol) and a solution of 9*E*-β-ionylideneacetaldehyde (**3a**, 698 mg, 3.2 mmol) in THF (3 mL), successively. After removal of cooling bath, the resulting mixture was stirred for 20 min and to this mixture was added a solution of NaN(TMS)$_2$ (4.96 mL, 1.0 M in THF, 4.96 mmol) at room temperature. After stirring for an additional 50 min, the reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL) and the organics were extracted with ether (2×60 mL), followed by a standard workup. The residue was purified by CC (hexane) to give the acetylene (**12**, 477 mg, 70%) as an yellow oil.

UV–vis λ_{max} nm: 283; IR ν_{max} cm^{-1}: 3306, 2096, 1613; ^{1}H NMR (300 MHz) δ: 1.01 (6H, s), 1.44–1.48 (2H, m), 1.57–1.64 (2H, m), 1.69 (3H, s), 2.01 (2H, t, $J = 6$ Hz), 2.08 (3H, s), 3.28 (1H, s), 5.40 (1H, s), 6.08 (1H, d, $J = 16$ Hz), 6.28 (1H, d, $J = 16$ Hz); HRMS (EI) m/z: Calcd for $C_{16}H_{22}$ (M^+) 214.1720. Found: 214.1708.

4.1.10. (1*E*,3*E*,5*E*)-1-Tributylstannyl-4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatriene (14). To a stirred suspension of CuCN (84 mg, 0.93 mmol) in THF (3 mL) was added a solution of BuLi (1.17 mL, 1.60 M in hexane, 1.87 mmol) at −40 °C. After stirring for an additional 15 min, tributyltinhydride (0.50 mL, 2.64 mmol) was added, and the resulting mixture was stirred for an additional 30 min. To this mixture was added a solution of the acetylenic compound (**12**, 200 mg, 0.93 mmol) in THF (2 mL) was added at −40 °C, and the resulting mixture was stirred for an additional 15 min. The reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL) and the organics were extracted with ether (2×60 mL), followed by a standard workup. The crude product was used for the next reaction without further purification.

^{1}H NMR (300 MHz) δ: 0.86–0.99 (15H, m), 1.01 (6H, s), 1.30 (6H, sext, $J = 7$ Hz), 1.42–1.53 (8H, m), 1.57–1.64 (2H, m), 1.70 (3H, s), 1.95 (3H, s), 2.02 (2H, t, $J = 6$ Hz), 6.05 (1H, d, $J = 16$ Hz), 6.06 (1H, d, $J = 11$ Hz), 6.17 (1H, d, $J = 16$ Hz), 6.29 (1H, d, $J = 18$ Hz), 6.92 (1H, dd, $J = 18$, 11 Hz).

4.1.11. (3*Z*,5*E*)-4-Methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3,5-hexadien-1-yne (13). This was prepared from the 9*Z*-aldehyde (**3′a**, 580 mg, 3.2 mmol) and (Ph_3PCH_2I)I (1.76 g, 3.33 mmol) in the same manner as described for the preparation of **12** in 30% yield (170 mg) as a pale yellow oil.

UV–vis λ_{max} nm: 291; IR ν_{max} cm^{-1}: 3306, 2087, 1611; ^{1}H NMR (300 MHz) δ: 1.04 (6H, s), 1.45–1.49 (2H, m), 1.58–1.66 (2H, m), 1.75 (3H, s), 1.95 (3H, s), 2.03 (2H, t, $J = 6.5$ Hz), 3.16 (1H, d, $J = 3$ Hz), 5.33 (1H, s), 6.34 (1H, d, $J = 16.5$ Hz), 6.81 (1H, d, $J = 16.5$ Hz); HRMS (EI) m/z: Calcd for $C_{16}H_{22}$ (M^+) 214.1720. Found: 214.1737.

4.1.12. (1*E*,3*Z*,5*E*)-1-Tributylstannyl-4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatriene (15). This was prepared from the acetylenic compound (**13**, 220 mg, 1.0 mmol) in the same manner as described for the preparation of the tetraenylstannane **14**, and used for the next coupling reaction without further purification.

4.2. General procedure for the preparation of enol triflates (16b–e)

To a stirred suspension of NaH (60% dispersion in oil, 1.1 mmol) in THF (3 mL) was added ethyl acetoacetate (1.0 equiv) at 0 °C. After stirring for an additional 10 min, a solution of BuLi (1.60 M in hexane, 1.05 equiv) was added and the resulting mixture was stirred for 10 min. To this mixture was added alkyl halide (1.0 equiv), and after stirring for 30 min, a solution of Tf_2NPh (1.0 equiv) in DMF (10 mL) was added. The resulting mixture was allowed to come to room temperature and stirred for 18 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL) and the organics were extracted with ether (2×60 mL), followed by a standard workup. The residue was purified by CC (hexane-ether = 9:1 as an eluent) to give the *E*-triflate as an colorless oil, stereoselectively.

4.2.1. Ethyl (*E*)-3-trifluoromethanesulfonyloxy-2-pentenoate (16b). This was prepared from NaH (264 mg, 11.0 mmol), ethyl acetoacetate (1.95 g, 15.0 mmol), *n*-BuLi (10.4 mL, 15.8 mmol), MeI (1.56 g, 11.0 mmol), and Tf_2NPh (3.57 g, 10.0 mmol) in 49% (1.34 g).

UV–vis λ_{max} nm: 203; IR ν_{max} cm^{-1}: 1722; ^1H NMR (300 MHz) δ: 1.21 (3H, t, $J = 7$ Hz), 1.31 (3H, t, $J = 7$ Hz), 2.94 (2H, q, $J = 7$ Hz), 4.22 (2H, q, $J = 7$ Hz), 5.92 (1H, s); HRMS (EI) *m/z*: Calcd for $C_8H_{11}F_3O_5S$ (M^+) 276.0278. Found: 276.0279.

4.2.2. Ethyl (*E*)-3-trifluoromethanesulfonyloxy-2-hexenoate (16c). This was prepared from NaH (396 mg, 16.5 mmol), ethyl acetoacetate (1.30 g, 10.0 mmol), *n*-BuLi (6.56 mL, 10.5 mmol), EtI (2.57 g, 16.5 mmol), and Tf_2NPh (5.36 g, 15.0 mmol) in 34% (1.46 g).

UV–vis λ_{max} nm: 201; IR ν_{max} cm^{-1}: 1721; ^1H NMR (300 MHz) δ: 0.99 (3H, t, $J = 7$ Hz), 1.31 (3H, t, $J = 7$ Hz), 1.65 (2H, sext, $J = 7$ Hz), 2.90 (2H, t, $J = 7$ Hz), 4.22 (2H, q, $J = 7$ Hz), 5.95 (1H, s); HRMS (EI) *m/z*: Calcd for $C_9H_{13}F_3O_5S$ (M^+) 290.0435. Found: 290.0442.

4.2.3. Ethyl (*E*)-3-trifluoromethanesulfonyloxy-2-heptenoate (16d). This was prepared from NaH (396 mg, 16.5 mmol), ethyl acetoacetate (1.95 g, 15.0 mmol), *n*-BuLi (10.4 mL, 15.8 mmol), PrBr (2.03 g, 16.5 mmol), and Tf_2NPh (5.36 g, 15.0 mmol) in 32% (1.45 g).

UV–vis λ_{max} nm: 198; IR ν_{max} cm^{-1}: 1721; ^1H NMR (300 MHz) δ: 0.94 (3H, t, $J = 7$ Hz), 1.31 (3H, t, $J = 7$ Hz), 1.38 (2H, sext, $J = 7$ Hz), 1.60 (2H, quint, $J = 7$ Hz), 2.92 (2H, t, $J = 7$ Hz), 4.22 (2H, q, $J = 7$ Hz), 5.93 (1H, s); HRMS (EI) *m/z*: Calcd for $C_{10}H_{15}F_3O_5S$ (M^+) 304.0591. Found: 304.0591.

4.2.4. Ethyl (*E*)-3-trifluoromethanesulfonyloxy-5-phenyl-2-hexenoate (16e). This was prepared from NaH (264 mg, 11.0 mmol), ethyl acetoacetate (1.30 g, 10.0 mmol), *n*-BuLi (6.56 mL, 10.5 mmol), $PhCH_2Br$ (1.88 g, 11.0 mmol), and Tf_2NPh (3.57 g, 10.0 mmol) in 33% (1.15 g).

UV–vis λ_{max} nm: 203; IR ν_{max} cm^{-1}: 1721, 1604; ^1H NMR (300 MHz) δ: 1.28 (3H, t, $J = 7$ Hz), 2.92 (2H, t, $J = 8$ Hz), 3.22 (2H, t, $J = 8$ Hz), 4.18 (2H, q, $J = 7$ Hz), 5.94 (1H, s), 7.20–7.32 (5H, m, Ar-H); HRMS (EI) *m/z*: Calcd for $C_{14}H_{15}F_3O_5S$ (M^+) 352.0592. Found: 352.0598.

4.3. General procedure for the preparation of ethyl retinoates and analogs (17a–e, 18a–e)

To a stirred solution of the triflate (**16**, 200 mg, 1 mmol) in DMF–THF (4 mL, 1:3), was added $Pd_2(dba)_3{\cdot}CHCl_3$ (40 mg, 0.034 mmol, 0.05 equiv) and Ph_3As (0.20 equiv) at room temperature under nitrogen. After 10 min, a solution of tetraenyl-tributylstannane (**14** or **15**, 300–400 mg, ca. 1 mmol, 1.5 equiv) in DMF–THF (3 mL, 2:1) was added and the resulting mixture was stirred for 30 min. The reaction was quenched with saturated aqueous NaCl (5 mL) and extracted with Et_2O (20 mL × 3), followed by a standard workup. The residue was purified by CC (ether–hexane = 1:9 as an eluent) to give the coupled product (**17** or **18**) as a pale yellow oil.

4.3.1. Ethyl (all-*E*)-retinoate (17a). This was prepared from the stannylolefin **14** prepared from the *E*-acetylenic compound (**12**, 200 mg, 0.93 mmol) and the triflate (**16a**, 245 mg, 0.93 mmol) in 60% yield (183 mg, two steps) as a pale yellow oil. The spectral data of this compound was identical with those of the literature.[5c]

4.3.2. Ethyl (2*E*,4*E*,6*E*,8*E*)-3-ethyl-7-methyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoate (17b). This was prepared from the stannylolefin **14** prepared from the *E*-acetylenic compound (**12**, 200 mg, 0.93 mmol) and the triflate (**16b**, 258 mg, 0.93 mmol) in 65% yield (207 mg, two steps) as a pale yellow oil.

UV–vis λ_{max} nm: 359; IR ν_{max} cm^{-1}: 1699, 1606; ^1H NMR (300 MHz) δ: 1.03 (6H, s), 1.15 (3H, t, $J = 7$ Hz), 1.29 (3H, t, $J = 7$ Hz), 1.44–1.48 (2H, m), 1.56–1.66 (2H, m), 1.71 (3H, s), 2.00 (3H, s), 2.05 (2H, t, $J = 6$ Hz), 2.86 (2H, q, $J = 7$ Hz), 4.17 (2H, q, $J = 7$ Hz), 5.71 (1H, s), 6.13 (1H, d, $J = 16.5$ Hz), 6.15 (1H, d, $J = 11.5$ Hz), 6.19 (1H, d, $J = 15$ Hz), 6.27 (1H, d, $J = 16.5$ Hz), 7.01 (1H, dd, $J = 15$, 11.5 Hz); ^{13}C NMR (75 MHz) δ: 12.87, 14.16, 14.28, 19.17, 21.00, 21.67, 28.90 (2C), 33.04, 34.21, 39.55, 59.54, 117.46, 128.57, 129.61, 129.91, 130.47, 133.77, 137.24, 137.67, 139.37, 159.10, 166.63; HRMS (EI) *m/z*: Calcd for $C_{23}H_{34}O_2$ (M^+) 342.2557. Found: 342.2566.

4.3.3. Ethyl (2*E*,4*E*,6*E*,8*E*)-7-methyl-3-propyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoate (17c). This was prepared from the stannylolefin **14** prepared from the *E*-acetylenic compound (**12**, 200 mg, 0.93 mmol) and the triflate (**16c**, 271 mg, 0.93 mmol) in 66% yield (219 mg, two steps) as a pale yellow oil.

IR ν_{max} cm^{-1}: 1699, 1604; ^1H NMR (300 MHz) δ: 1.01 (2H, t, $J = 7$ Hz), 1.03 (6H, s), 1.29 (3H, t, $J = 7$ Hz), 1.44–1.49 (2H, m), 1.54–1.64 (4H, m), 1.71 (3H, s), 2.00 (3H, s), 2.02 (2H, t, $J = 6$ Hz), 2.81 (2H, q, $J = 7$ Hz), 4.17 (2H, q, $J = 7$ Hz), 5.72 (1H, s), 6.13 (1H, d, $J = 16$ Hz), 6.14 (1H, d, $J = 11$ Hz), 6.20 (1H, d, $J = 15$ Hz), 6.27 (1H, d, $J = 16$ Hz), 7.00 (1H, dd, $J = 15$, 11 Hz); ^{13}C NMR (75 MHz) δ: 12.84, 14.28, 14.31, 19.17, 21.66, 23.11, 28.90 (2C), 29.64, 33.04, 34.20, 39.55, 59.53, 117.92, 128.54, 129.60, 129.90, 130.50, 134.25, 137.24, 137.66, 139.31, 157.50, 166.75; HRMS (EI) *m/z*: Calcd for $C_{24}H_{36}O_2$ (M^+) 356.2713. Found: 356.2731.

4.3.4. Ethyl (2*E*,4*E*,6*E*,8*E*)-3-butyl-7-methyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoate (17d). This was prepared from the stannylolefin **14** prepared

from the *E*-acetylenic compound (**12**, 200 mg, 0.93 mmol) and the triflate (**16d**, 284 mg, 0.93 mmol) in 44% yield (150 mg, two steps) as a pale yellow oil.

UV–vis λ_{max} nm: 357; IR ν_{max} cm^{-1}: 1698, 1604; ^1H NMR (300 MHz) δ: 0.95 (2H, t, $J = 7$ Hz), 1.03 (6H, s), 1.29 (3H, t, $J = 7$ Hz), 1.40–1.52 (4H, m), 1.57–1.65 (4H, m), 1.71 (3H, s), 2.00 (3H, s), 2.02 (2H, t, $J = 6.5$ Hz), 2.83 (2H, q, $J = 7$ Hz), 4.16 (2H, q, $J = 7$ Hz), 5.73 (1H, s), 6.13 (1H, d, $J = 16$ Hz), 6.14 (1H, d, $J = 11$ Hz), 6.19 (1H, d, $J = 15$ Hz), 6.27 (1H, d, $J = 16$ Hz), 7.00 (1H, dd, $J = 15$, 11 Hz); ^{13}C NMR (75 MHz) δ: 12.84, 13.92, 14.30, 19.17, 21.67, 23.02, 27.50, 28.90 (2C), 31.95, 33.04, 34.21, 39.54, 59.53, 117.79, 128.54, 129.60, 129.90, 130.50, 134.21, 137.24, 137.67, 139.32, 157.76, 166.72; HRMS (EI) *m/z*: Calcd for $C_{25}H_{38}O_2$ (M^+) 370.2870. Found: 370.2870.

4.3.5. Ethyl (2*E*,4*E*,6*E*,8*E*)-7-methyl-3-(2-phenyl)ethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoate (17e). This was prepared from the stannylolefin **14** prepared from the *E*-acetylenic compound (**12**, 200 mg, 0.93 mmol) and the triflate (**16e**, 329 mg, 0.93 mmol) in 65% yield (253 mg, two steps) as a pale yellow oil.

UV–vis λ_{max} nm: 357; IR ν_{max} cm^{-1}: 1698, 1604; ^1H NMR (300 MHz) δ: 1.03 (6H, s), 1.29 (3H, t, $J = 7$ Hz), 1.45–1.49 (2H, m), 1.58–1.66 (2H, m), 1.72 (3H, s), 1.99 (3H, s), 2.05 (2H, t, $J = 6.5$ Hz), 2.80 (2H, t, $J = 8.5$ Hz), 3.14 (2H, t, $J = 8.5$ Hz), 4.18 (2H, q, $J = 7$ Hz), 5.78 (1H, s), 6.14 (1H, d, $J = 16.5$ Hz), 6.15 (1H, d, $J = 11$ Hz), 6.22 (1H, d, $J = 15$ Hz), 6.29 (1H, d, $J = 16.5$ Hz), 7.01 (1H, dd, $J = 15$, 11 Hz), 7.20–7.34 (5H, m); ^{13}C NMR (75 MHz) δ: 12.88, 14.33, 19.17, 21.69, 28.91 (2C), 30.11, 33.06, 34.21, 35.95, 39.57, 59.65, 118.24, 125.92, 128.33 (2C), 128.44 (2C), 128.74, 129.49, 130.00, 130.78, 133.74, 137.18, 137.67, 139.61, 142.00, 156.46, 166.58; HRMS (EI) *m/z*: Calcd for $C_{29}H_{38}O_2$ (M^+) 418.2870. Found: 418.2868.

4.3.6. Ethyl (9*Z*)-retinoate (18a). This was prepared from the stannylolefin **15** prepared from the *Z*-acetylenic compound (**13**, 189 mg, 0.93 mmol) and the triflate (**16a**, 231 mg, 0.88 mmol) in 39% yield (113 mg, two steps) as a pale yellow oil. The spectral data of this compound was identical with those of literature.[5c]

4.3.7. Ethyl (2*E*,4*E*,6*Z*,8*E*)-3-ethyl-7-methyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoate (18b). This was prepared from the stannylolefin **15** prepared from the *Z*-acetylenic compound (**13**, 169 mg, 0.79 mmol) and the triflate (**16b**, 218 mg, 0.79 mmol) in 45% yield (121 mg, two steps) as a pale yellow oil.

IR ν_{max} cm^{-1}: 1700, 1585; ^1H NMR (300 MHz) δ: 1.04 (6H, s), 1.14 (3H, t, $J = 7$ Hz), 1.29 (3H, t, $J = 7$ Hz), 1.44–1.49 (2H, m), 1.59–1.66 (2H, m), 1.75 (3H, s), 2.00 (3H, s), 2.04 (2H, t, $J = 6.5$ Hz), 2.86 (2H, q, $J = 7$ Hz), 4.16 (2H, q, $J = 7$ Hz), 5.71 (1H, s), 6.05 (1H, d, $J = 11.5$ Hz), 6.12 (1H, d, $J = 15$ Hz), 6.27 (1H, d, $J = 16$ Hz), 6.65 (1H, d, $J = 16$ Hz), 7.10 (1H, dd, $J = 15$, 11.5 Hz); ^{13}C NMR (75 MHz) δ: 14.08, 14.28, 19.15, 20.80, 21.05, 21.76, 28.94 (2C), 33.06, 34.18, 39.48, 59.54, 117.37, 128.06, 129.36, 129.47, 130.00, 130.12, 132.95, 137.92, 138.20, 159.10, 166.63; HRMS (EI) *m/z*: Calcd for $C_{23}H_{34}O_2$ (M^+) 342.2557. Found: 342.2556.

4.3.8. Ethyl (2*E*,4*E*,6*Z*,8*E*)-7-methyl-3-propyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoate (18c). This was prepared from the stannylolefin **15** prepared from the *Z*-acetylenic compound (**13**, 180 mg, 0.84 mmol) and the triflate (**16c**, 240 mg, 0.84 mmol) in 48% yield (143 mg, two steps) as a pale yellow oil.

UV–vis λ_{max} nm: 353; IR ν_{max} cm^{-1}: 1699, 1586; ^1H NMR (300 MHz) δ: 0.99 (2H, t, $J = 7.5$ Hz), 1.05 (6H, s), 1.27 (3H, t, $J = 7$ Hz), 1.43–1.49 (2H, m), 1.52–1.64 (4H, m), 1.76 (3H, s), 1.99 (3H, s), 2.05 (2H, t, $J = 6$ Hz), 2.82 (2H, q, $J = 7.5$ Hz), 4.15 (2H, q, $J = 7$ Hz), 5.73 (1H, s), 6.04 (1H, d, $J = 11.5$ Hz), 6.12 (1H, d, $J = 15$ Hz), 6.28 (1H, d, $J = 16$ Hz), 6.66 (1H, d, $J = 16$ Hz), 7.09 (1H, dd, $J = 15$, 11.5 Hz); ^{13}C NMR (75 MHz) δ: 14.29 (2C), 19.15, 20.76, 21.73, 23.07, 28.94 (2C), 29.69, 33.13, 34.16, 39.58, 59.50, 117.83, 128.03, 129.32, 129.44, 129.88, 130.37, 133.36, 137.80, 138.20, 157.52, 166.70; HRMS (EI) *m/z*: Calcd for $C_{24}H_{36}O_2$ (M^+) 356.2713. Found: 356.2707.

4.3.9. Ethyl (2*E*,4*E*,6*Z*,8*E*)-3-butyl-7-methyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoate (18d). This was prepared from the stannylolefin **15** prepared from the *Z*-acetylenic compound (**13**, 200 mg, 0.93 mmol) and the triflate (**16d**, 250 mg, 0.93 mmol) in 58% yield (253 mg, two steps) as a pale yellow oil.

UV–vis λ_{max} nm: 354; IR ν_{max} cm^{-1}: 1698, 1586; ^1H NMR (300 MHz) δ: 0.94 (2H, t, $J = 7.5$ Hz), 1.06 (6H, s), 1.28 (3H, t, $J = 7$ Hz), 1.41–1.51 (4H, m), 1.58–1.68 (4H, m), 1.75 (3H, s), 2.00 (3H, s), 2.05 (2H, t, $J = 6.5$ Hz), 2.83 (2H, q, $J = 7.5$ Hz), 4.18 (2H, q, $J = 7$ Hz), 5.73 (1H, s), 6.05 (1H, d, $J = 11.5$ Hz), 6.12 (1H, d, $J = 15$ Hz), 6.29 (1H, d, $J = 16.5$ Hz), 6.67 (1H, d, $J = 16.5$ Hz), 7.10 (1H, dd, $J = 15$, 11.5); ^{13}C NMR (75 MHz) δ: 13.88, 14.29, 19.14, 20.75, 21.70, 23.08, 27.56, 28.94 (2C), 31.95, 33.15, 34.16, 39.61, 59.51, 117.68, 128.00, 129.26, 129.47, 129.93, 130.43, 133.31, 137.79, 138.24, 157.79, 166.72; HRMS (EI) *m/z*: Calcd for $C_{25}H_{38}O_2$ (M^+) 370.2870. Found: 370.2878.

4.3.10. Ethyl (2*E*,4*E*,6*Z*,8*E*)-7-methyl-3-(2-phenyl)ethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoate (18e). This was prepared from the stannylolefin **15** prepared from the *Z*-acetylenic compound (**13**, 200 mg, 0.93 mmol) and the triflate (**16e**, 329 mg, 0.93 mmol) in 57% yield (221 mg, two steps) as a pale yellow oil.

UV–vis λ_{max} nm: 350, 205; IR ν_{max} cm^{-1}: 1698, 1586; ^1H NMR (300 MHz) δ: 1.06 (6H, s), 1.30 (3H, t, $J = 7$ Hz), 1.49–1.55 (2H, m), 1.60–1.68 (2H, m), 1.76 (3H, s), 2.01

(3H, s), 2.05 (2H, t, $J = 6.5$ Hz), 2.78 (2H, t, $J = 8.5$ Hz), 3.11 (2H, t, $J = 8.5$ Hz), 4.18 (2H, q, $J = 7$ Hz), 5.78 (1H, s), 6.07 (1H, d, $J = 12$ Hz), 6.16 (1H, d, $J = 15$ Hz), 6.30 (1H, d, $J = 16.5$ Hz), 6.65 (1H, d, $J = 16.5$ Hz), 7.15 (1H, dd, $J = 15$, 12 Hz), 7.21–7.32 (5H, m); ^{13}C NMR (75 MHz) δ: 14.34, 19.18, 20.81, 21.78, 28.96 (2C), 30.34, 33.10, 34.21, 35.97, 39.55, 59.65, 118.21, 125.93, 128.32 (2C), 128.42 (2C), 127.92, 129.35, 129.64, 130.21, 130.26, 132.85, 137.89, 138.53, 142.04, 156.46, 166.58; HRMS (EI) m/z: Calcd for $C_{29}H_{38}O_2$ (M^+) 418.2870. Found: 418.2873.

4.4. General procedure for preparation of retinoic acid and its analogs

A mixture of the ester (**17** or **18**, 0.4 mmol) and 10% KOH (3 mL) in EtOH (5 mL) was heated at 50 °C for several hours. After cooling, the reaction mixture was made acidic by 5% HCl (7 mL) at 0 °C, and the organic was extracted with AcOEt (10 mL × 2), followed by a standard workup. The residue was purified by CC (ether–hexane = 3:7 as an eluent) to give the acid (**1** or **2**) as a pale yellow solid, which was recrystallized from the solvent indicated as follows.

4.4.1. (all-*E*)-Retinoic acid (1a). This was prepared from the ester (**17a**, 33 mg, 0.10 mmol) in 83% yield (26 mg) as a pale yellow solid. The spectral data of this compound was identical with those of the literature.[5c]

4.4.2. (2*E*,4*E*,6*E*,8*E*)-3-Ethyl-7-methyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid (1b). This was prepared from the ester (**17b**, 49 mg, 0.14 mmol) in 67% yield (31 mg) as a pale yellow solid.

Mp 120–121 °C (AcOEt–hexane); UV–vis λ_{max} nm (ε): 340 (40,000); IR ν_{max} cm^{-1}: 1679, 1576; ^{1}H NMR (300 MHz) δ: 1.03 (6H, s), 1.16 (3H, t, $J = 7$ Hz), 1.43–1.48 (2H, m), 1.56–1.65 (2H, m), 1.72 (3H, s), 2.02 (3H, s), 2.03 (2H, t, $J = 6$ Hz), 2.89 (2H, q, $J = 7$ Hz), 5.74 (1H, s), 6.15 (1H, d, $J = 16$ Hz), 6.17 (1H, d, $J = 11.5$ Hz), 6.22 (1H, d, $J = 15$ Hz), 6.30 (1H, d, $J = 16$ Hz), 7.07 (1H, dd, $J = 15$, 11.5 Hz), COOH signal was not observed; ^{13}C NMR (125 MHz) δ: 12.95, 14.29, 19.21, 21.15, 21.73, 28.95 (2C), 33.11, 34.26, 39.61, 116.35, 129.00, 129.55, 130.12, 131.44, 133.56, 137.21, 137.70, 140.12, 161.17, 171.01; HRMS (EI) m/z: Calcd for $C_{21}H_{30}O_2$ (M^+) 314.2245. Found: 314.2255.

4.4.3. (2*E*,4*E*,6*E*,8*E*)-7-Methyl-3-propyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid (1c). This was prepared from the ester (**17c**, 80 mg, 0.23 mmol) in 83% yield (62 mg) as a pale yellow solid.

Mp 114–115 °C (AcOEt–hexane); UV–vis λ_{max} nm (ε): 340 (40,400); IR ν_{max} cm^{-1}: 1681, 1577; ^{1}H NMR (300 MHz) δ: 1.01 (2H, t, $J = 7$ Hz), 1.04 (6H, s), 1.46–1.49 (2H, m), 1.53–1.66 (4H, m), 1.72 (3H, s), 2.01 (3H, s), 2.03 (2H, t, $J = 6$ Hz), 2.86 (2H, q, $J = 7$ Hz), 5.78 (1H, s), 6.15 (1H, d, $J = 16$ Hz), 6.16 (1H, d, $J = 11.5$ Hz), 6.23 (1H, d, $J = 15$ Hz), 6.30 (1H, d, $J = 16$ Hz), 7.06 (1H, dd, $J = 15$, 11.5 Hz), COOH signal was not observed; ^{13}C NMR (125 MHz) δ: 12.94, 14.31, 19.21, 21.73, 23.23, 28.95 (2C), 29.69, 33.11, 34.26, 39.61, 116.84, 128.98, 129.54, 130.42, 131.47, 134.05, 137.23, 138.00, 140.06, 160.15, 171.36; HRMS (EI) m/z: Calcd for $C_{22}H_{32}O_2$ (M^+) 328.2401. Found: 328.2391.

4.4.4. (2*E*,4*E*,6*E*,8*E*)-3-Butyl-7-methyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid (1d). This was prepared from the ester (**17d**, 63 mg, 0.14 mmol) quantitatively (58 mg) as a pale yellow solid.

Mp 103–105 °C (AcOEt–hexane); UV–vis λ_{max} nm (ε): 340 (40,900); IR ν_{max} cm^{-1}: 1678, 1576; ^{1}H NMR (300 MHz) δ: 0.96 (3H, t, $J = 7$ Hz), 1.04 (6H, s), 1.42–1.52 (4H, m), 1.58–1.66 (4H, m), 1.72 (3H, s), 2.01 (3H, s), 2.03 (2H, t, $J = 6$ Hz), 2.88 (2H, q, $J = 7$ Hz), 5.76 (1H, s), 6.15 (1H, d, $J = 16$ Hz), 6.17 (1H, d, $J = 11.5$ Hz), 6.23 (1H, d, $J = 15$ Hz), 6.30 (1H, d, $J = 16$ Hz), 7.07 (1H, dd, $J = 15$, 11.5 Hz), COOH signal was not observed; ^{13}C NMR (125 MHz) δ: 12.93, 13.89, 19.21, 21.72, 22.98, 27.56, 28.95 (2C), 32.06, 33.10, 34.27, 39.60, 116.62, 128.99, 129.53, 130.11, 131.48, 133.99, 137.22, 137.70, 140.09, 160.49, 171.20; HRMS (EI) m/z: Calcd for $C_{23}H_{34}O_2$ (M^+) 342.2557. Found: 342.2564.

4.4.5. (2*E*,4*E*,6*E*,8*E*)-7-Methyl-3-(2-phenyl)ethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid (1e). This was prepared from the ester (**17e**, 74 mg, 0.18 mmol) in 82% yield (56 mg) as a pale yellow solid.

Mp 147–149 °C (AcOEt–hexane); UV–vis λ_{max} nm (ε): 340 (40,600); IR ν_{max} cm^{-1}: 1682, 1585; ^{1}H NMR (300 MHz) δ: 1.07 (6H, s), 1.48–1.52 (2H, m), 1.61–1.68 (2H, m), 1.75 (3H, s), 2.03 (3H, s), 2.06 (2H, t, $J = 5.5$ Hz), 2.85 (2H, t, $J = 7.5$ Hz), 3.19 (2H, t, $J = 7.5$ Hz), 5.86 (1H, s), 6.18 (1H, d, $J = 16$ Hz), 6.19 (1H, d, $J = 11$ Hz), 6.29 (1H, d, $J = 15$ Hz), 6.34 (1H, d, $J = 16$ Hz), 7.10 (1H, dd, $J = 15$, 11 Hz), 7.21–7.34 (5H, m), COOH signal was not observed; ^{13}C NMR (125 MHz) δ: 12.98, 19.21, 21.74, 28.96 (2C), 30.33, 33.13, 34.28, 36.09, 39.62, 116.77, 126.05, 128.43 (2C), 128.45 (2C), 129.22, 129.41, 130.25, 131.82, 133.48, 137.15, 137.69, 140.45, 141.89, 159.24, 170.27; HRMS (EI) m/z: Calcd for $C_{27}H_{34}O_2$ (M^+) 390.2557. Found: 390.2564.

4.4.6. (9*Z*)-Retinoic acid (2a). This was prepared from the ester (**18a**, 90 mg, 0.27 mmol) in 98% yield (83 mg) as a pale yellow solid. The spectral data of this compound was identical with those of the literature.[5c]

4.4.7. (2*E*,4*E*,6*Z*,8*E*)-3-Ethyl-7-methyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid (2b). This was prepared from the ester (**18b**, 90 mg, 0.26 mmol) quantitatively (85 mg) as a pale yellow solid.

Mp 135–137 °C (AcOEt–hexane); UV–vis λ_{max} nm (ε): 340 (37,700); IR ν_{max} cm^{-1}: 1680, 1578; ^1H NMR (300 MHz) δ: 1.06 (6H, s), 1.15 (3H, t, $J = 7.5$ Hz), 1.48–1.52 (2H, m), 1.61–1.68 (2H, m), 1.76 (3H, s), 2.02 (3H, s), 2.06 (2H, t, $J = 6$ Hz), 2.88 (2H, q, $J = 7.5$ Hz), 5.75 (1H, s), 6.07 (1H, d, $J = 11.5$ Hz), 6.16 (1H, d, $J = 15$ Hz), 6.30 (1H, d, $J = 16$ Hz), 6.67 (1H, d, $J = 16$ Hz), 7.16 (1H, dd, $J = 15$, 11.5 Hz), COOH signal was not observed; ^{13}C NMR (125 MHz) δ: 14.19, 19.21, 20.89, 21.21, 21.81, 28.99 (2C), 33.11, 34.24, 39.53, 116.11, 128.00, 129.44, 130.29, 130.31, 130.41, 132.74, 137.96, 138.99, 161.72, 170.50; HRMS (EI) m/z: Calcd for $C_{21}H_{30}O_2$ (M^+) 314.2244. Found: 314.2255.

4.4.8. (2*E*,4*E*,6*Z*,8*E*)-7-Methyl-3-propyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid (2c). This was prepared from the ester (**18c**, 85 mg, 0.24 mmol) in 93% yield (73 mg) as a pale yellow solid.

Mp 139–141 °C (AcOEt–hexane); UV–vis λ_{max} nm (ε): 340 (38,700); IR ν_{max} cm^{-1}: 1679, 1578; ^1H NMR (300 MHz) δ: 0.99 (2H, t, $J = 7.5$ Hz), 1.06 (6H, s), 1.47–1.51 (2H, m), 1.53–1.65 (4H, m), 1.76 (3H, s), 2.01 (3H, s), 2.06 (2H, t, $J = 6.5$ Hz), 2.84 (2H, q, $J = 7.5$ Hz), 5.77 (1H, s), 6.06 (1H, d, $J = 11.5$ Hz), 6.16 (1H, d, $J = 15$ Hz), 6.30 (1H, d, $J = 16$ Hz), 6.67 (1H, d, $J = 16$ Hz), 7.15 (1H, dd, $J = 15$, 11.5 Hz), COOH signal was not observed; ^{13}C NMR (125 MHz) δ: 14.30, 19.20, 20.86, 21.79, 23.17, 29.01 (2C), 29.75, 33.20, 34.24, 39.64, 116.58, 127.94, 129.29, 130.31, 130.41, 130.56, 133.15, 137.84, 139.03, 160.16, 170.78; HRMS (EI) m/z: Calcd for $C_{22}H_{32}O_2$ (M^+) 328.2401. Found: 328.2411.

4.4.9. (2*E*,4*E*,6*Z*,8*E*)-3-Butyl-7-methyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid (2d). This was prepared from the ester (**18d**, 79 mg, 0.21 mmol) in 95% yield (70 mg) as a pale yellow solid.

Mp 109–111 °C (AcOEt–hexane); UV–vis λ_{max} nm (ε): 340 (34,900); IR ν_{max} cm^{-1}: 1679, 1580; ^1H NMR (300 MHz) δ: 0.94 (3H, t, $J = 7$ Hz), 1.06 (6H, s), 1.42–1.52 (4H, m), 1.60–1.68 (4H, m), 1.76 (3H, s), 2.01 (3H, s), 2.06 (2H, t, $J = 6.5$ Hz), 2.86 (2H, q, $J = 7$ Hz), 5.75 (1H, s), 6.07 (1H, d, $J = 11.5$ Hz), 6.16 (1H, d, $J = 15$ Hz), 6.31 (1H, d, $J = 16$ Hz), 6.68 (1H, d, $J = 16$ Hz), 7.16 (1H, dd, $J = 15$, 11.5 Hz), COOH signal was not observed; ^{13}C NMR (125 MHz) δ: 13.87, 19.19, 20.85, 21.75, 23.03, 27.65, 29.00 (2C), 32.03, 33.20, 34.26, 39.65, 116.23, 127.91, 129.22, 130.36, 130.51, 130.61, 133.04, 137.82, 139.14, 160.67, 170.54; HRMS (EI) m/z: Calcd for $C_{23}H_{34}O_2$ (M^+) 342.2557. Found: 342.2563.

4.4.10. (2*E*,4*E*,6*Z*,8*E*)-7-Methyl-3-(2-phenyl)ethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic acid (2e). This was prepared from the ester (**18e**, 90 mg, 0.22 mmol) in 91% yield (77 mg) as a pale yellow solid.

Mp 128–131 °C (AcOEt–hexane); UV–vis λ_{max} nm (ε): 340 (36,900), 210 (12,881); IR ν_{max} cm^{-1}: 1680, 1579; ^1H NMR (300 MHz) δ: 1.08 (6H, s), 1.50–1.54 (2H, m), 1.62–1.71 (2H, m), 1.78 (3H, s), 2.04 (3H, s), 2.08 (2H, t, $J = 6$ Hz), 2.81 (2H, t, $J = 8.5$ Hz), 3.15 (2H, t, $J = 8.5$ Hz), 5.84 (1H, s), 6.10 (1H, d, $J = 11.5$ Hz), 6.22 (1H, d, $J = 15$ Hz), 6.34 (1H, d, $J = 16.5$ Hz), 6.68 (1H, d, $J = 16.5$ Hz), 7.22 (1H, dd, $J = 15$, 11.5 Hz), 7.27–7.34 (5H, m), COOH signal was not observed; ^{13}C NMR (125 MHz) δ: 19.21, 20.89, 21.82, 29.01 (2C), 30.56, 33.16, 34.26, 36.09, 39.60, 116.84, 126.05, 127.85, 128.41 (2C), 128.44 (2C), 129.31, 130.49, 130.64, 130.67, 132.62, 137.92, 139.42, 141.93, 159.25, 170.67; HRMS (EI) m/z: Calcd for $C_{27}H_{34}O_2$ (M^+) 390.2557. Found: 390.2562.

4.5. Biological assay

4.5.1. HL-60 cells and synchronization of cell cycle at S phase by excess amounts of thymidine. HL-60 cells were maintained in continuous culture in RPMI-1640 medium (Nissui Seiyaku Co., Ltd, Tokyo, Japan) supplemented with 10% dextran-coated charcoal-treated fetal calf serum (FCS) (Gibco BRL, Grand Island, NY, USA), and kanamycin (0.06 mg/mL) (Sigma, St. Louis, MO, USA) at 37 °C in a humidified atmosphere of 5% CO_2 in air. The doubling time of HL-60 cells was approximately 24 h. For synchronization at S phase, cells (4×10^5 cells/mL) were cultured in 30 mL of RPMI-1640 medium supplemented with 2.5 mM thymidine. After washing with Ca, Mg-free phosphate-buffered saline (PBS) [PBS(−)] twice, the synchronization of cell cycle was repeated in the same manner, and the cells thus obtained were used in the biological assays.

4.5.2. Flow cytometry. Cells (10^5 cells/well) were placed in 24-well tissue culture plates and cultured for 3 days with retinoids (10^{-10}–10^{-6} M) in RPMI-1640 medium at 37 °C in a humidified atmosphere of 5% CO_2 in air. To reduce the effects of contact inhibition, control cells were adjusted to 60–70% confluency at the time of FACS analysis. Each group of cells was collected in PBS(−). Then, the cells were resuspended in PBS(−) containing 0.2% Triton-X and 1 μg/μL RNase, and incubated at 37 °C for 1 h. Cells were washed with PBS(−) and incubated with 0.5 mL of DNA-staining solution containing propidium iodide (50 μg/mL) at 4 °C for 20 min. The cells were analyzed with a flow cytometer equipped with an argon laser (488 nm, Becton Dickinson FACScan™) and cell cycle distribution was analyzed by ModiFiT LT (Verity).

4.5.3. Cell surface antigen expression analysis. Cells (10^5 cells/well) were placed in 24-well tissue culture plates, and cultured for 3 days in RPMI-1640 medium with retinoids (10^{-10}–10^{-6} M) under the same conditions as described in the flow cytometry. Each group of cells was then collected and washed with PBS(−) once. Then, the cells (2×10^5 cells) were resuspended in 100 μL diluent solution containing 1% bovine serum albumin (BSA) and 1% sodium azide and incubated with 10 μL human

monoclonal FITC conjugated CD 11b antibody and CD14 antibody (Sigma) for 30 min at room temperature. The cells were washed once with diluent solution and then fixed in 300 μL of PBS(−) containing 2% paraformaldehyde. Fluorescence was detected on a Becton Dickinson FACScan™ at excitation wavelength of 490 nm and emission wavelength of 520 nm. Results were recorded as the mean fluorescence index, which is the product of the % fluorescence and the mean fluorescenced intensity, with 10^4 cells being counted per treatment.

4.5.4. DNA fragmentation assay. For assessment of quantitative DNA fragmentation (laddering), DNA was isolated from cells of each culture, and was examined for fragmentation. DNA was electrophoresed in a 2% agarose gel that was stained with ethidium bromide for observation under ultraviolet light.

4.5.5. Transfection and luciferase activity assay. Human osteosarcoma MG-63 cells, which are positive for RXR gene expression, were maintained in Dulbecco's modification Eagle medium (Gibco BRL) supplemented with 1% penicillin, 1% streptomycin, and 10% dextran-coated charcoal-treated FCS (Gibco BRL). Cells (2×10^5) were suspended in 2 mL of medium and transfected with 1.0 μg of a one-hybrid plasmid (pM vector, Promega Corp., Madison, WI, USA) containing a human RXRα cDNA connected with a yeast GAL4 DNA-binding domain cDNA (GAL-DBD), 0.5 μg of luciferase reporter plasmid (pGVP2 vector, Toyo Ink Co., Ltd) containing GAL-4 binding site (GAL-BS) and a pRL-CMV vector as an internal control using the Tfx-50 reagent (Promega Corp.). The cells were incubated with retinoids (10^{-6} M) for 2 days. The luciferase activities of the cell lysates were measured with a luciferase assay system (Toyo Ink Co., Ltd), according to the manufacture's instructions. Transactivation measured by luciferase activity was standardized with the luciferase activity of the same cells determined by the Sea Pansy luciferase assay system as a control (Toyo Ink Co. Ltd) Each set of experiments was repeated at least three times, and the results are presented in terms of fold induction as means ± SE.

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