Synthesis of 9Z-9-Substituted Retinoic Acids by Palladium Catalyzed Coupling Reaction of a Vinyl Triflate with Alkenyl Stannanes

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Received May 12, 2000; accepted June 29, 2000

Palladium catalyzed cross coupling reactions of a vinyl triflate intermediate and various alkenyl stannanes afforded trisubstituted *Z*-olefins stereoselectively in high yields. These olefins were then converted to the corresponding 9*Z*-retinoic acids *via* Horner–Emmons reaction and subsequent basic hydrolysis in excellent yields.

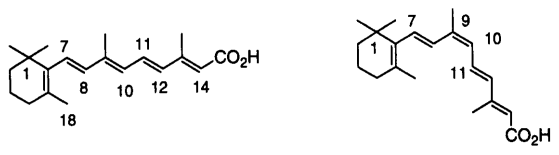
Key words retinoid X receptor; 9*Z*-retinoic acid analog; coupling reaction; vinyl triflate; alkenyl stannane

It is well known that all-*E*-retinoic acid **1** and 9*Z*-retinoic acid **2** are the ligands of retinoic acid receptors (RARα, β, γ) and retinoid X receptors (RXRα, β, γ), respectively.[1] These receptors are members of the nuclear receptor superfamily and exhibit significant biological functions including cell differentiation, cell proliferation, embryonic development, *etc.* through gene transcription.[2] Currently, much effort is being directed at the preparation of receptor-selective retinoids in order to define the functions of each receptor and to develop therapeutic agents.[3] In connection with our study on the stereoselective synthesis of retinoids and carotenoids,[4] we wish to describe here a novel synthesis of 9-substituted 9*Z*-retinoic acids using a palladium catalyzed cross-coupling reaction.[5]

Treatment of 2,6,6-trimethyl-1-cyclohexene-1-acetaldehyde **3**,[6] prepared by Wittig reaction of β-cyclocitral with (methoxymethyl)triphenylphosphonium chloride followed by hydrolysis, with *N*-phenyltrifluoromethanesulfonimide (Tf_2NPh) in the presense of potassium *tert*-butoxide gave the vinyl triflate **4** in 58% yield as the only stereoisomer. In a preliminary study, palladium catalyzed coupling of **4** with alkenyl stannane **6a**[7] under various conditions indicated that the best results were obtained using 5 mol% tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) as catalyst at room temperature in dimethylformamide (DMF) for 2 h, to produce alcohol **9a** in 87% yield. The structure of **9a** was determined after oxidation to the aldehyde **10a** and comparison of spectral data with those in the literature.[8] However, under similar conditions the reaction of **4** with alkenyl stannanes **7** or **8** having an electron withdrawing group did not proceed and the expected coupling product was not obtained.

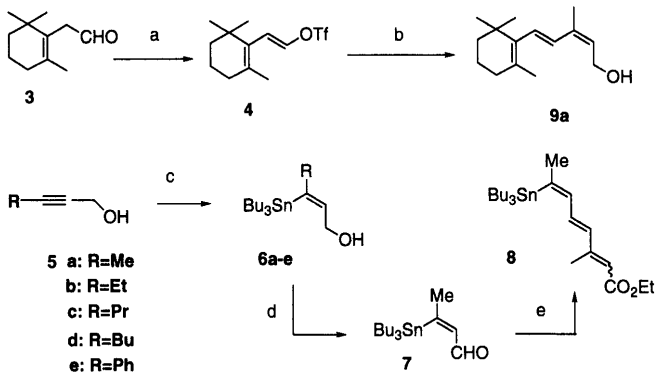
In order to determine the generality of this coupling, we examined the reaction of **4** with various alkenyl stannanes (**6b—d**), prepared from substituted propargyl alcohols **5** according to the previously reported method,[7] and the results are listed in Table 1.

In the case of **6e**, the yield was decreased dramatically (run 5), however, the yield was improved using tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3) with triphenylarsine ($AsPh_3$) as ligand[9] at room temperature with the prolonged reaction time (overnight). Oxidation of alcohols **9** with tetra-*n*-propyl ammonium per-ruthenate (TPAP)/*N*-methyl morpholine *N*-oxide (NMO)[10] afforded the trienals **10** in good yields. The Horner–Emmons reaction of **10** with C5-phosphonate was carried out using *n*-BuLi as a base to



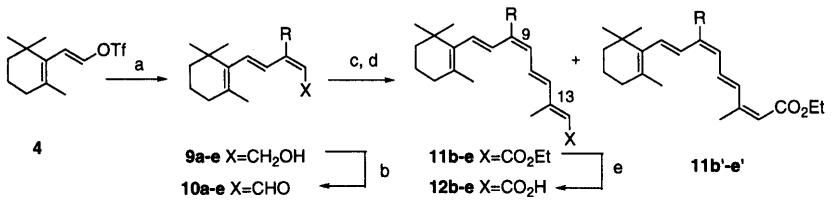
1 all-*E*-Retinoic acid 2 9*Z*-Retinoic Acid

Chart 1



Reagents: a) *t*-BuOK, Tf_2NPh / THF, 0°C; b) $Pd(PPh_3)_4$, **6a** / DMF, r.t.; c) $LiAlH_4$ then Bu_3SnOMe / THF, 0°C; d) MnO_2 / CH_2Cl_2, r.t.; e) $(EtO)_2P(O)CH_2C(Me)=CHCO_2Et$, *n*-BuLi / THF, 0°C

Chart 2



Reagents: a) $Pd(PPh_3)_4$, **6** / DMF, r.t.; b) TPAP, NMO / CH_2Cl_2, r.t.; c) $(EtO)_2P(O)CH_2C(Me)=CHCO_2Et$, *n*-BuLi / THF, 0°C; d) prep. HPLC; e) 10% KOH-EtOH, 50°C

Chart 3

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Table 1. Yields in the Synthesis of 9-Substituted 9*Z*-Retinoic Acids

Run	Substituent R	Yield of **9** (%)[a]	Yield of **10** (%)	Yield of **11** (%, 13*E*/13*Z*)	Yield of **12** (%)
1	Me	87	72	—[b]	—[b]
2	Et	88	87	80/16	95
3	Pr	87	75	53/23	Quant.
4	Bu	83	71	70/21	Quant.
5	Ph[c]	43 (Quant.)[d]	71	52/12	91

a) 10 mol% of $Pd(PPh_3)_4$ in DMF at r.t. for 2 h. *b*) Ref. 8. *c*) The stereochemistry at 9 position is *E*. *d*) Pd_2dba_3, $AsPh_3$ in DMF at r.t. for 14 h.

give esters **11** as a mixture of double bond isomers [13*E* : 13*Z*=*ca.* 3 : 2—5 : 1]. After separation of the 9*Z*,13*E*-isomers by preparative high-performance liquid chromatography (HPLC), these compounds were transformed to the corresponding acids **12** by basic hydrolysis in excellent yields.

In summary, we have developed a novel method for the stereoselective synthesis of trisubstituted *Z*-olefin using the palladium catalyzed coupling reaction of a vinyl triflate with alkenyl stannanes and have achieved the synthesis of 9-substituted 9*Z*-retinoic acids **12**.[11] Biological investigations with these compounds are ongoing.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. UV spectra were recorded on a JASCO Ubest-55 instrument and IR spectra on a Perkin-Elmer FT-IR Paragon 1000 spectrometer. ^{1}H-NMR spectra were obtained on a Varian Gemini-200 or Gemini-300 NMR spectrometer. Mass spectra were determined on a Hitachi M-4100 instrument. Column chromatography (CC) under aspirator pressure (*ca.* 30 mmHg) was performed using Merck Silica gel 60. Preparative HPLC was conducted on a Shimadzu LC-6A instrument with a Shimadzu UV-VIS detector, SPD-6AV, using a LiChrosorb Si-60 column (5 μm), 1.0×30 cm. All reactions were carried out under a nitrogen atmosphere. THF and ether were purified by distillation from benzophenone–sodium ketyl under nitrogen. Materials obtained from commercial suppliers were used without further purification except when otherwise noted. Diisopropylamine was purified by distillation from CaH_2. 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 a rotary evaporator.

(*E*)-2-(2,6,6-Trimethylcyclohexen-1-yl)-ethenyl (trifluoromethyl)sulfonate (4) A solution of the aldehyde (**3**, 1.01 g, 6.1 mmol)[6] in THF (12 ml) was added to a stirred solution of *tert*-BuOK (2 g, 9.0 mmol) in THF (10 ml) at 0 °C. The mixture was stirred for 15 min at 0 °C, and *N*-phenyl trifluoromethanesulfonimide (2.6 g, 4.2 mmol) was added at the same temperature. After stirring for an additional 30 min at room temperature, the reaction was quenched with saturated aqueous NH_4Cl (30 ml) and extracted with Et_2O (50 ml×3), followed by standard work up. The residue was purified by CC (ether : hexane=1 : 4 as eluent) to give the enol triflate (**4**, 1.03 g, 58%) as a colorless oil. UV λ_{max} (EtOH) nm: 235; IR ($CHCl_3$) cm^{-1}: 2934, 2868, 1645, 1423, 1215, 1110; ^{1}H-NMR (300 MHz) δ: 0.98 (6H, s), 1.43—1.66 (4H, m), 1.69 (3H, s), 2.02 (2H, br t, *J*=6 Hz), 6.22 (1H, d, *J*=12 Hz), 6.41 (1H, d, *J*=12 Hz); HR-MS *m/z*: 298.1944 (Calcd for $C_{20}H_{26}O_2$: 298.1944).

General Procedure for the Preparation of 3-Substituted-3-tributylstannyl-prop-2-en-1-ols (6a—e) NaOMe (0.16 g, 0.19 mmol) was added to a solution of $LiAlH_4$ (1.0 mol THF solution, 43.5 ml, 43.5 mmol) at 0 °C. The mixture was cooled to 0 °C and 3-substituted prop-2-en-1-ol (20 mmol) in THF (5 ml) was slowly added. The resulting mixture was stirred 1 h at 0 °C, then EtOAc (7.3 ml) was added and the mixture stirred for 15 min at room temperature. The reaction mixture was then cooled to 0 °C, Bu_3SnOMe (11.5 ml, 39.8 mmol) was added and the resulting mixture was left at room temperature. After 2 d, MeOH (30 ml) was added and the mixture was stirred for 1 h at room temperature and poured into H_2O (700 ml). The mixture was carefully made acidic by addition of dilute HCl and the product was extracted with Et_2O (80 ml×3), followed by standard work up. The residue was purified by CC (ether : hexane=1 : 4 as eluent) to give stannyl alcohol (**6**) as a colorless oil.

(2*Z*)-3-Tributylstannyl-2-buten-1-ol (**6a**): Prepared from 2-butyn-1-ol (**5a**, 1.68 g, 24 mmol) in 79% yield (6.58 g) as a colorless oil. The spectral data of this compound were identical with those in the literature.[7]

(2*Z*)-3-Tributylstannyl-2-penten-1-ol (**6b**): Prepared from 2-pentyn-1-ol (**5b**, 1.63 g, 19 mmol) in 62% yield (4.49 g) as a colorless oil. IR ($CHCl_3$) cm^{-1}: 3607, 3453, 2958, 2927, 1463, 1377; ^{1}H-NMR (300 MHz) δ: 0.88—1.59 (30H, m), 1.15 (1H, t, *J*=6 Hz), 2.24 (2H, q, *J*=7.5 Hz), 4.05 (2H, m), 6.25 (1H, t, *J*=6.5 Hz, $^3J_{Sn-H,trans}$=127 Hz). HR-MS *m/z*: 376.1767 (Calcd for $C_{17}H_{36}OSn$: 376.1786).

(2*Z*)-3-Tributylstannyl-2-hexen-1-ol (**6c**): Prepared from 2-hexyn-1-ol (**5c**, 1.91 g, 20 mmol) in 78% yield (5.92 g) as a colorless oil. IR ($CHCl_3$) cm^{-1}: 3608, 3448, 2958, 2927, 1463, 1377; ^{1}H-NMR (300 MHz) δ: 0.87—1.59 (32H, m), 1.14 (1H, t, *J*=5.5 Hz), 2.19 (2H, t, *J*=7.5 Hz), 4.05 (2H, m), 6.23 (1H, t, *J*=6.5 Hz, $^3J_{Sn-H,trans}$=126 Hz); HR-MS *m/z*: 390.1917 (Calcd for $C_{18}H_{38}OSn$: 390.1942).

(2*Z*)-3-Tributylstannyl-2-hepten-1-ol (**6d**): Prepared from 2-heptyn-1-ol (**5c**, 2.25 g, 20 mmol) in 74% yield (5.99 g) as a colorless oil. IR ($CHCl_3$) cm^{-1}: 3608, 3451, 2958, 2928, 1464, 1378; ^{1}H-NMR (300 MHz) δ: 0.88—1.59 (34H, m), 1.15 (1H, t, *J*=6.5 Hz), 2.20 (2H, t, *J*=7 Hz), 4.05 (2H, m), 6.22 (1H, t, *J*=6.5 Hz, $^3J_{Sn-H,trans}$=129 Hz); HR-MS *m/z*: 404.2074 (Calcd for $C_{19}H_{40}OSn$: 404.2099).

(2*Z*)-3-Tributylstannyl-3-phenyl-2-buten-1-ol (**6e**): Prepared from 3-phenyl-2-butyn-1-ol (**5e**, 1.42 g, 11 mmol) in 80% yield (3.65 g) as a colorless oil. The spectral data were identical with those in the literature.[7]

General Procedure for the Preparation of 9*Z*-Aldehyde (9a—e) To a stirred solution of triflate (**4**, 200 mg, 0.67 mmol) in DMF (2 ml) was added $Pd(PPh_3)_4$ (40 mg, 0.034 mmol, 0.05 eq) at room temperature under nitrogen. After 10 min, a solution of tributylstannyl olefin (**5**, 300—400 mg, *ca.* 1 mmol, 1.5 eq) in DMF (2 ml) was added and the resulting mixture was stirred for 20 min. The reaction was quenched with saturated aqueous NaCl (5 ml) and extracted with Et_2O (10 ml×3), followed by the standard work up. The residue was purified by CC (ether : hexane=1 : 4 to 3 : 7 as an eluent) to give the coupled alcohol (**9**). The alcohol (**9**, 0.5 mmol) was dissolved in CH_2Cl_2 (5 ml) containing 4 Å sieves and NMO (0.1 ml, 0.75 mmol). After stirring the mixture for 10 min, TPAP (0.025 mmol) was added and the reaction followed by TLC until complete. When complete, the mixture was diluted with CH_2Cl_2 (20 ml) and washed with sodium sulphite solution (10 ml), brine (10 ml) and finally saturated copper(II) sulphate solution (10 ml). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by CC (ether : hexane=1 : 4 as eluent) to give the aldehyde (**9**) as a pale yellow oil.

(2*Z*)-3-Methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienal (**9a**): Prepared from triflate (**4**, 170 mg, 0.57 mmol) and stannylolefin (**6a**, 320 mg, 0.9 mmol) in 63% yield (79 mg, 2 steps) as a colorless oil. The spectral data were identical with those in the literature.[8]

(2*Z*)-3-Ethyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienal (**9b**): Prepared from triflate (**4**, 98 mg, 0.33 mmol) and stannylolefin (**6b**, 188 mg, 0.5 mmol) in 76% yield (59 mg, 2 steps) as a colorless oil. UV λ_{max} (EtOH) nm: 326sh, 282; IR ($CHCl_3$) cm^{-1}: 2933, 1655, 1607; ^{1}H-NMR (300 MHz) δ: 1.05 (6H, s), 1.19 (3H, d, *J*=7.5 Hz), 1.46—1.69 (4H, m), 1.75 (3H, s), 2.06 (2H, br t, *J*=6 Hz), 2.48 (2H, q, *J*=7.5 Hz), 5.89 (1H, d, *J*=8 Hz), 6.61 (1H, d, *J*=16 Hz), 6.89 (1H, d, *J*=16 Hz), 10.15 (1H, d, *J*=8 Hz); HR-MS *m/z*: 232.1819 (Calcd for $C_{16}H_{24}O$: 232.1825).

(2*Z*)-3-Propyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienal (**9c**): Prepared from triflate (**4**, 105 mg, 0.35 mmol) and stannylolefin (**6c**, 195 mg, 0.5 mmol) in 65% yield (56 mg, 2 steps) as a colorless oil. UV λ_{max} (EtOH) nm: 321sh, 279.5; IR ($CHCl_3$) cm^{-1}: 2934, 1659, 1612; ^{1}H-NMR (300 MHz) δ: 0.97 (3H, t, *J*=7.5 Hz), 1.04 (6H, s), 1.46—1.69 (6H, m), 1.73 (3H, s), 2.04 (2H, br t, *J*=6 Hz), 2.39 (2H, t, *J*=7 Hz), 5.86 (1H, d, *J*=8 Hz), 6.58 (1H, d, *J*=16 Hz), 6.85 (1H, d, *J*=16 Hz), 10.11 (1H, d, *J*=8 Hz); HR-MS *m/z*: 246.1987 (Calcd for $C_{17}H_{26}O$: 246.1983).

(2*Z*)-3-Butyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienal (**9d**): Prepared from triflate (**4**, 122 mg, 0.41 mmol) and stannylolefin (**6d**, 227 mg,

0.56 mmol) in 59% yield (62 mg, 2 steps) as a colorless oil. UV λ_{max} (EtOH) nm: 319, 267; IR ($CHCl_3$) cm^{-1}: 2959, 1657, 1611; ^{1}H-NMR (300 MHz) δ: 0.95 (3H, t, J=7.5 Hz), 1.06 (6H, s), 1.48—1.65 (8H, m), 1.75 (3H, s), 2.06 (2H, br t, J=6 Hz), 2.43 (2H, t, J=7.5 Hz), 5.89 (1H, d, J=8 Hz), 6.60 (1H, d, J=16 Hz), 6.87 (1H, d, J=16 Hz), 10.11 (1H, d, J=8 Hz); HR-MS *m/z*: 260.2123 (Calcd for $C_{18}H_{28}O$: 260.2139).

(2*E*)-3-Phenyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-pentadienal (**9e**): Prepared from triflate (**4**, 93 mg, 0.31 mmol) and stannylolefin (**6e**, 213 mg, 0.5 mmol) in 31% yield (27 mg, 2 steps) as a colorless oil.

UV λ_{max} (EtOH) nm: 299.5; IR ($CHCl_3$) cm^{-1}: 2936, 1660, 1614; ^{1}H-NMR (300 MHz) δ: 1.04 (6H, s), 1.45—1.70 (4H, m), 1.79 (3H, s), 2.06 (2H, br t, J=6.5 Hz), 6.14 (1H, d, J=8 Hz), 6.45 (2H, d, J=16 Hz), 6.93 (1H, d, J=16 Hz), 7.43 (5H, br s), 10.14 (1H, d, J=8 Hz); HR-MS *m/z*: 280.1831 (Calcd for $C_{20}H_{24}O$: 280.1826).

General Procedure for the Preparation of Ethyl 9-Substituted Retinoate (11b—e) To a solution of diethyl 3-(methoxycarbonyl)-2-methyl-2-propenylphosphonate (E:Z=4:1) (391 mg, 2 mmol) in THF (5.5 ml) was added *n*-BuLi (1.6 M hexane solution, 1.25 ml, 2 mmol) at 0 °C. After stirring for 30 min, a solution of the aldehyde (**10**, *ca.* 0.7 mmol) in THF (5 ml) was added. The resulting mixture was stirred for an additional 5 h. The reaction was quenched with saturated NH_4Cl (5 ml) and extracted with ether followed by standard workup. The residue was purified by preparative HPLC (ether : benzene : hexane=1 : 25 : 74) to give the respective pentaenyl esters (**11**) as pale yellow oils.

Ethyl (2*E*/*Z*,4*E*,6*Z*,8*E*)-7-Ethyl-3-methyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,4,6,8-tetraenoates (**11b**) These were prepared from the aldehyde (**10b**, 66 mg, 0.28 mmol) in 80% (**11b**, 56 mg) and 16% (**11b′**, 15 mg) yields, respectively.

2*E*,6*Z*-isomer **11b**: UV λ_{max} (EtOH) nm: 349; IR ($CHCl_3$) cm^{-1}: 2932, 1698, 1589; ^{1}H-NMR (300 MHz) δ: 1.04 (6H, s), 1.15 (3H, t, J=7 Hz), 1.29 (3H, t, J=7 Hz), 1.4—1.7 (4H, m), 1.75 (3H, s), 2.05 (2H, t, J=6.5 Hz), 2.33 (3H, s), 2.34 (2H, t, J=7 Hz), 4.17 (2H, q, J=7 Hz), 5.77 (1H, s), 6.06 (1H, d, J=11.5 Hz), 6.24 (1H, d, J=15 Hz), 6.30 (1H, d, J=16.5 Hz), 6.53 (1H, d, J=16.5 Hz), 7.08 (1H, dd, J=11.5, 15 Hz); HR-MS *m/z*: 342.2566 (Calcd for $C_{23}H_{34}O_2$: 342.2557).

2*Z*,6*Z*-isomer **11b′**: UV λ_{max} (EtOH) nm: 350.5; IR ($CHCl_3$) cm^{-1}: 2931, 1696, 1601; ^{1}H-NMR (300 MHz) δ: 1.03 (6H, s), 1.14 (3H, t, J=7 Hz), 1.30 (3H, t, J=7 Hz), 1.4—1.7 (4H, m), 1.75 (3H, s), 2.04 (2H, t, J=6.5 Hz), 2.06 (3H, s), 2.34 (2H, t, J=7 Hz), 4.16 (2H, q, J=7 Hz), 5.64 (1H, s), 6.19 (1H, d, J=12 Hz), 6.27 (1H, d, J=16 Hz), 6.53 (1H, d, J=16 Hz), 7.03 (1H, dd, J=12, 15 Hz), 7.73 (1H, d, J=15 Hz); HR-MS *m/z*: 342.2563 (Calcd for $C_{23}H_{34}O_2$: 342.2557).

Ethyl (2*E*/*Z*,4*E*,6*Z*,8*E*)-3-Methyl-9-(2,6,6-trimethylcyclohexen-1-yl)-7-propylnona-2,4,6,8-tetraenoates (**11c**): These were prepared from the aldehyde (**10c**, 160 mg, 0.65 mmol) in 53% (**11c**, 122 mg) and 22% (**11c′**, 52 mg) yields, respectively.

2*E*,6*Z*-isomer **11c**: UV λ_{max} (EtOH) nm: 349; IR ($CHCl_3$) cm^{-1}: 2930, 1696, 1601; ^{1}H-NMR (300 MHz) δ: 0.94 (3H, t, J=7 Hz), 1.03 (6H, s), 1.28 (3H, t, J=7 Hz), 1.4—1.7 (6H, m), 1.73 (3H, s), 2.04 (2H, t, J=6.5 Hz), 2.31 (2H, t, J=7 Hz), 2.33 (3H, s), 4.16 (2H, q, J=7 Hz), 5.76 (1H, s), 6.04 (1H, d, J=11 Hz), 6.23 (1H, d, J=15 Hz), 6.28 (1H, d, J=16 Hz), 6.51 (1H, d, J=16 Hz), 7.07 (1H, dd, J=11, 15 Hz); HR-MS *m/z*: 356.2698 (Calcd for $C_{24}H_{36}O_2$: 356.2713).

2*Z*,6*Z*-isomer **11c′**: UV λ_{max} (EtOH) nm: 351.5; IR ($CHCl_3$) cm^{-1}: 2932, 1698, 1601; ^{1}H-NMR (300 MHz) δ: 0.90 (3H, t, J=7 Hz), 1.04 (6H, s), 1.28 (3H, t, J=7 Hz), 1.4—1.7 (6H, m), 1.74 (3H, s), 2.04 (2H, t, J=6.5 Hz), 2.05 (3H, s), 2.31 (2H, t, J=7 Hz), 4.16 (2H, q, J=7 Hz), 5.63 (1H, s), 6.15 (1H, d, J=12 Hz), 6.28 (1H, d, J=15 Hz), 6.51 (1H, d, J=16 Hz), 7.07 (1H, dd, J=11, 15 Hz), 7.73 (1H, d, J=16 Hz); HR-MS *m/z*: 356.2712 (Calcd for $C_{24}H_{36}O_2$: 356.2713).

Ethyl (2*E*/*Z*,4*E*,6*Z*,8*E*)-7-Butyl-3-methyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,4,6,8-tetraenoates (**11d**): These were prepared from the aldehyde (**10d**, 98 mg, 0.38 mmol) in 70% (**11d**, 97 mg) and 21% (**11d′**, 29 mg) yields, respectively.

2*E*,6*Z*-isomer **11d**: UV λ_{max} (EtOH) nm: 350, 244.5; IR ($CHCl_3$) cm^{-1}: 2932, 1699, 1602; ^{1}H-NMR (300 MHz) δ: 0.94 (3H, t, J=7 Hz), 1.05 (6H, s), 1.30 (3H, t, J=7 Hz), 1.4—1.7 (8H, m), 1.65 (3H, s), 2.06 (2H, t, J=6 Hz), 2.34 (2H, t, J=7 Hz), 2.35 (3H, s), 4.18 (2H, q, J=7 Hz), 5.77 (1H, s), 6.05 (1H, d, J=11.5 Hz), 6.24 (1H, d, J=15 Hz), 6.29 (1H, d, J=16 Hz), 6.52 (1H, d, J=16 Hz), 7.07 (1H, dd, J=11.5, 15 Hz); HR-MS *m/z*: 370.2883 (Calcd for $C_{25}H_{38}O_2$: 370.2870).

2*Z*,6*Z*-isomer **11d′**: UV λ_{max} (EtOH) nm: 350, 244.5; IR ($CHCl_3$) cm^{-1}: 2933, 1698, 1589; ^{1}H-NMR (300 MHz) δ: 0.90 (3H, t, J=7 Hz), 1.05 (6H, s), 1.29 (3H, t, J=7 Hz), 1.4—1.7 (8H, m), 1.75 (3H, s), 2.04 (2H, t, J=6.5 Hz), 2.05 (3H, s), 2.34 (2H, t, J=7 Hz), 4.17 (2H, q, J=7 Hz), 5.64 (1H, s), 6.15 (1H, d, J=11 Hz), 6.28 (1H, d, J=16 Hz), 6.51 (1H, d, J=16 Hz), 7.07 (1H, dd, J=11, 15 Hz), 7.73 (1H, d, J=15 Hz); HR-MS *m/z*: 370.2884 (Calcd for $C_{25}H_{38}O_2$: 370.2870).

Ethyl (2*E*/*Z*,4*E*,6*E*,8*E*)-3-Methyl-9-(2,6,6-trimethylcyclohexen-1-yl)-7-phenylnona-2,4,6,8-tetraenoates (**11e**): These were prepared from the aldehyde (**10e**, 69 mg, 0.25 mmol) in 52% (**11e**, 49 mg) and 12% (**11e′**, 12 mg) yields, respectively.

2*E*,6*E*-isomer **11e**: UV λ_{max} (EtOH) nm: 360, 286, 246; IR ($CHCl_3$) cm^{-1}: 2933, 1698, 1606; ^{1}H-NMR (300 MHz) δ: 1.02 (6H, s), 1.30 (3H, t, J=7 Hz), 1.4—1.7 (4H, m), 1.81 (3H, s), 2.05 (2H, t, J=6 Hz), 2.38 (3H, s), 4.19 (2H, q, J=7 Hz), 5.81 (1H, s), 6.18 (1H, d, J=16 Hz), 6.26 (1H, d, J=11.5 Hz), 6.37 (1H, d, J=15 Hz), 6.68 (1H, d, J=16 Hz), 7.19 (1H, dd, J=11.5, 15 Hz); HR-MS *m/z*: 390.2566 (Calcd for $C_{27}H_{34}O_2$: 390.2557).

2*Z*,6*E*-isomer **11e′**: UV λ_{max} (EtOH) nm: 362, 291, 248; IR ($CHCl_3$) cm^{-1}: 2930, 1670, 1602; ^{1}H-NMR (300 MHz) δ: 1.00 (6H, s), 1.29 (3H, t, J=7 Hz), 1.4—1.7 (4H, m), 1.79 (3H, s), 2.05 (2H, t, J=6.5 Hz), 2.09 (3H, s), 4.17 (2H, q, J=7 Hz), 5.68 (1H, s), 6.18 (1H, d, J=16 Hz), 6.39 (1H, d, J=11 Hz), 6.65 (1H, d, J=16 Hz), 7.17 (1H, dd, J=11, 15 Hz), 7.73 (1H, d, J=15 Hz); HR-MS *m/z*: 390.2563 (Calcd for $C_{27}H_{34}O_2$: 390.2557).

General Procedure for the Preparation of 9*Z*-Retinoic Acid Analogs (12b—e) A mixture of the ester (**11**, *ca.* 40 mg, 0.1 mmol) and 25% NaOH solution (5 ml) in methanol (5 ml) was heated at 50 °C for 30 min. After cooling, the reaction mixture was made acidic with 5% HCl, and the organics were extracted with ethyl acetate followed by standard workup. The residue was purified by CC (ethyl acetate : hexane=3 : 1 as eluent) to give the acid (**12**, 23 mg, 98%) as a yellow solid.

(2*E*,4*E*,6*Z*,8*E*)-7-Ethyl-3-methyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,4,6,8-tetraenoic Acid (**12b**): Prepared from the ester (**11b**, 43 mg, 0.13 mmol) in 95% (38 mg) yield. mp 125—127 °C (ether–*n*-hexane); UV λ_{max} (EtOH) nm: 339; IR ($CHCl_3$) cm^{-1}: 3300—2600, 1681, 1586; ^{1}H-NMR (300 MHz) δ: 1.04 (6H, s), 1.15 (3H, t, J=7.5 Hz), 1.4—1.7 (4H, m), 1.75 (3H, s), 2.05 (2H, t, J=7 Hz), 2.35 (3H, s), 2.38 (2H, t, J=7.5 Hz), 5.79 (1H, s), 6.07 (1H, d, J=12 Hz), 6.27 (1H, d, J=16 Hz), 6.32 (1H, d, J=15 Hz), 6.53 (1H, d, J=16 Hz), 7.13 (1H, dd, J=12, 15 Hz); a COOH signal was not present; HR-MS *m/z*: 314.2251 (Calcd for $C_{21}H_{30}O_2$: 314.2244).

(2*E*,4*E*,6*Z*,8*E*)-3-Methyl-9-(2,6,6-trimethylcyclohexen-1-yl)-7-propylnona-2,4,6,8-tetraenoic Acid (**12c**): Prepared from the ester (**11c**, 58 mg, 0.16 mmol) in quantitative (53 mg) yield. mp 125—127 °C (ether–*n*-hexane); UV λ_{max} (EtOH) nm: 340; IR ($CHCl_3$) cm^{-1}: 3350—2600, 1679, 1586; ^{1}H-NMR (300 MHz) δ: 0.94 (3H, t, J=7 Hz), 1.03 (6H, s), 1.4—1.7 (6H, m), 1.74 (3H, s), 2.04 (2H, t, J=6.5 Hz), 2.32 (2H, t, J=7 Hz), 2.34 (3H, s), 5.79 (1H, s), 6.05 (1H, d, J=11 Hz), 6.25 (1H, d, J=15 Hz), 6.29 (1H, d, J=16 Hz), 6.51 (1H, d, J=16 Hz), 7.12 (1H, dd, J=11, 15 Hz); a COOH signal was not present; HR-MS *m/z*: 328.2416 (Calcd for $C_{22}H_{32}O_2$: 328.2401).

(2*E*,4*E*,6*Z*,8*E*)-7-Butyl-3-methyl-9-(2,6,6-trimethylcyclohexen-1-yl)nona-2,4,6,8-tetraenoic Acid (**12d**): Prepared from the ester (**10d**, 23 mg, 0.06 mmol) in quantitative (21 mg) yield. mp 135—136 °C (ether–*n*-hexane); UV λ_{max} (EtOH) nm: 345.5; IR ($CHCl_3$) cm^{-1}: 3300—2600, 1678, 1585; ^{1}H-NMR (300 MHz) δ: 0.94 (3H, t, J=7 Hz), 1.04 (6H, s), 1.4—1.7 (8H, m), 1.76 (3H, s), 2.06 (2H, t, J=6 Hz), 2.34 (2H, t, J=7 Hz), 2.35 (3H, s), 5.80 (1H, s), 6.06 (1H, d, J=11.5 Hz), 6.27 (1H, d, J=15 Hz), 6.31 (1H, d, J=16 Hz), 6.52 (1H, d, J=16 Hz), 7.14 (1H, dd, J=11.5, 15 Hz); a COOH signal was not present; HR-MS *m/z*: 342.2572 (Calcd for $C_{23}H_{34}O_2$: 342.2557).

(2*E*,4*E*,6*E*,8*E*)-3-Methyl-9-(2,6,6-trimethylcyclohexen-1-yl)-7-phenylnona-2,4,6,8-tetraenoic Acid (**12e**): Prepared from the ester (**11e**, 23 mg, 0.06 mmol) in 91% (20 mg) yield. mp 148—150 °C (ether–*n*-hexane); UV λ_{max} (EtOH) nm: 339; IR ($CHCl_3$) cm^{-1}: 3300—2600, 1681, 1603, 1583; ^{1}H-NMR (300 MHz) δ: 1.00 (6H, s), 1.4—1.7 (4H, m), 1.79 (3H, s), 2.05 (2H, t, J=6 Hz), 2.37 (3H, s), 5.70 (1H, s), 6.17 (1H, d, J=16 Hz), 6.27 (1H, d, J=11 Hz), 6.37 (1H, d, J=15 Hz), 6.67 (1H, d, J=16 Hz), 7.23 (1H, dd, J=11, 15 Hz); a COOH signal was not present; HR-MS *m/z*: 362.2260 (Calcd for $C_{25}H_{30}O_2$: 362.2244).

Acknowledgment This work was supported in part by the Kobe Pharmaceutical University Collaboration Fund and The Science Research Promotion Fund from the Japan Private School Promotion Foundation.

References and Notes

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11) According to nomenclature, **12e** is the 9*E*-isomer.