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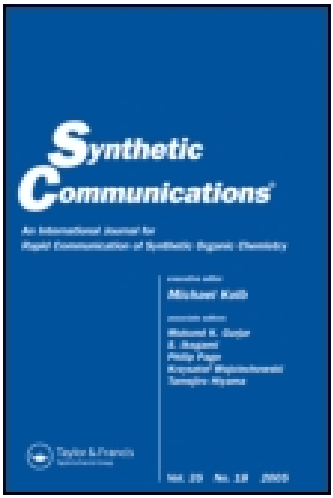

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Synthesis of New 9-Methylene Analogs of Retinoids

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Synthesis of New 9-Methylene Analogs of Retinoids

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Abstract: We report herein a series of syntheses that provides diverse structural modifications of the side-chain of retinoids to obtain new compounds with potential use in anticancer therapy. Starting from a β-methylenealdehyde synthon, we have synthesized a series of new 9-methylene-13-desmethyl-14-methyl analogs and a series of 9-methylene-11-desmethyl trienic homologs. For the first series, the condensation of the C-15 β-methylenealdehyde with the anion of ethyl 4-(diethoxyphosphoryl)-2*E*-methylbut-2-enoate led to the 7*E*,11*E*,13*E*-ester. This gave the desired aldehyde by a reduction into the corresponding alcohol (DIBAL-H) and subsequent oxidation by MnO_2. For the second series, the reaction of the C-15 β-methylenealdehyde with the anions of ethyl diethoxyphosphorylacetate, diethyl cyanomethylphosphonate, or diethyl 2-oxopropylphosphonate led to the C-17 ester, the C-17 nitrile, and the C-18 ketone, respectively.

Keywords: β-Methylenealdehyde, retinoic acid analogs, retinoids

Retinoic acids (*all E* and 9*Z*), metabolites of retinol, act as ligands of small molecular hormones that regulate the gene transcription through the activation

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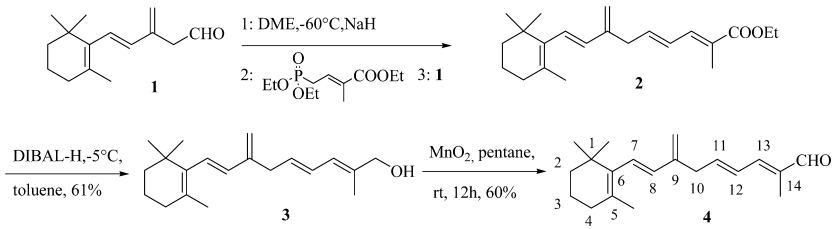
of the retinoic acid receptors (RARα, β, and γ) and retinoid X receptors (RXRα, β, and γ). These receptors show major biological functions such as cell differentiation, cell proliferation, and embryonic development. *All E*-retinoic acid (ATRA), 13-*cis*-retinoic acid (13-*cis*-RA) and synthetic etretinate have been used for treatment of skin diseases.[1–3] Retinoids are compounds that regulate various physiological processes throughout embryogenesis, organogenesis, and homeostasis. Their differentiation and apoptosis-inducing properties have shown strong utility for the treatment of carcinomas and for cancer chemoprevention.[4–6]

Aromatic triethylenic compounds that have activity as antagonists for retinoic acid receptors were described and their pharmaceutical compositions patented.[7] Another process related to the syntheses of aromatic retinoid antagonists for the manufacturing of a medicament for the treatment of osteoporosis and for use in the treatment of preneoplastic and neoplastic diseases. They were also tested for retinoid receptor antagonist activity.[8]

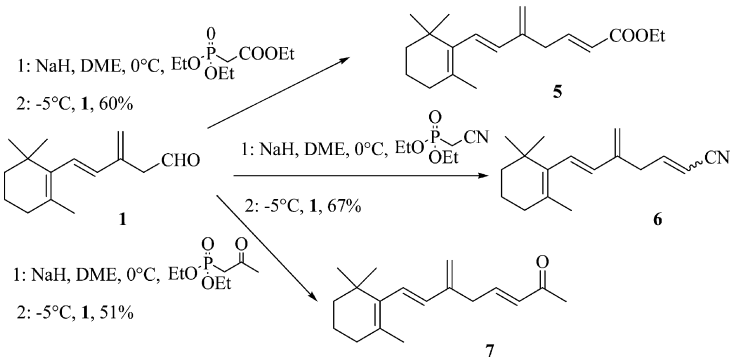
In a recent work, we described the syntheses and the differentiation and apoptosis-inducing potential of methylene and side-chain-modified retinoids.[9] Taking into account these data and in connection with structure–activity relationships of retinoids, a series of new 9-methylene-13-desmethyl-14-methyl analogs and a series of 9-methylene-11-desmethyl trienic homologs were synthesized. A β-methylenealdehyde synthon **1** (4*E*-3-methylene-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-4-pentenal) was used for these syntheses, which was previously reported for the syntheses of 13*E* and 13*Z* retinoids.[10] The synthesis of the first series of analogs is described in Scheme 1.

Horner–Emmons reaction of **1** with the anion of ethyl 4-(diethoxyphosphoryl)-2*E*-methylbut-2-enoate (generated by sodium hydride) led to the 7*E*,11*E*,13*E*-ester **2** in 41% yield (after purification), with a regioselectivity higher than 99% for the *all E* isomer. This latter was further reduced at -5°C in toluene into the corresponding 7*E*,11*E*,13*E*-alcohol **3**, using diisobutylaluminium hydride (DIBAL-H, 1M in toluene). A convenient oxidation with manganese dioxide in pentane at room temperature for 12 h led to the 7*E*,11*E*,13*E*-aldehyde **4** in 60% yield.

The second series of homologs is depicted in Scheme 2.



Scheme 1.



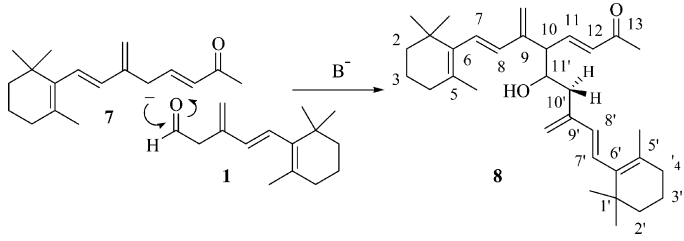
Scheme 2.

Horner–Emmons reaction of **1** with the anions of ethyl diethoxyphosphorylacetate, diethyl cyanomethylphosphonate, and diethyl 2-oxopropylphosphonate led to the compounds **5**–**7** in satisfactory yields (51–67%). For the syntheses of products **5** and **7**, the regioselectivity for the production of the 7*E*,9-methylene-11*E* isomer was higher than 99%.

During the synthesis of ketone **7**, we also isolated a small amount (13%) of a by-product: compound **8**. This formation could be explained by an aldolization reaction involving the anion of the ketone **7** and the β-methylenealdehyde **1** and catalyzed by the anion of the phosphonate (Scheme 3). This reaction was not possible in the case of compounds **5** and **6** because their phosphonate anions were extremely nucleophilic.

EXPERIMENTAL

All reactions were carried out under an argon atmosphere. ^{1}H NMR spectra were recorded at 400 MHz on a Bruker Avance DPX 400. Chemical shifts are reported in ppm (δ) relative to TMS. IR spectra were run on a Bruker IF 55 spectrometer.



Scheme 3.

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2. At -60°C, 6.6 g of ethyl 4-(diethoxyphosphoryl)-2-methylbut-2-enoate[11] (10.1 mmol) in 25 mL of 1,2-dimethoxyethane (DME) were slowly added to a stirred suspension of 0.4 g of sodium hydride (10.1 mmol) in 20 mL of DME. The phosphonate was synthesized by an Arbusov reaction between the bromide (or chloride) compound and triethylphosphite at 160°C. After 20 min at -60°C, 2 g of β-methyleneacetaldehyde (9.2 mmol) in 25 mL of DME were added, and the mixture was warmed to rt. After purification of the crude product (4.8 g) by column chromatography (SiO_2, cyclohexane/dichloromethane 60/40), the ester **2** was obtained as yellow oil (1.23 g, 41%).

IR (film cm^{-1}): 1717, 1601. ^{1}H NMR ($CDCl_3$): 7.22 (d, 1H, $J = 11.2$, C_{13}-H); 6.45 (dd, 1H, $J = 15.1$, $J = 11.2$, C_{12}-H); 6.19 (dt, 1H, $J = 15.1$, $J = 6.6$, C_{11}-H); 6.15 and 6.07 (2d, 2H, $J = 16.1$, C_7-H and C_8-H); 5.05 and 4.98 (2s, 2H, C_9-CH_2); 4.22 (q, 2H, $J = 7.2$, $CO_2CH_2CH_3$); 3.18 (d, 2H, $J = 6.6$, C_{10}-H); 2.01 (t, 2H, $J = 6.1$, C_4-H); 1.94 (1s, 3H, C_{14}-CH_3); 1.70 (1s, 3H, C_5-CH_3); 1.62 (m, 2H, C_3-H); 1.46 (m, 2H, C_2-H); 1.32 (t, 3H, $J = 7.2$, $CO_2CH_2CH_3$); 1.00 (s, 6H, C_1-CH_3). ^{13}C NMR ($CDCl_3$): 168.5 (C_{15}); 143.9, 137.3, 129.1, and 125.6 (C_1, C_2, C_9 and C_{14}); 139.9, 138.0, 134.2, 128.0, and 127.2 (C_7, C_8, C_{11}, C_{12}, and C_{13}); 115.4 (C_9-CH_2); 60.4 ($CO_2\underline{CH_2}CH_3$); 39.3, 36.0, 32.7, and 19.1 (C_3, C_4, C_5, and C_{10}); 34.1 (C_6); 28.7, 21.5, 14.2, and 12.5 (C_2-CH_3, C_6-CH_3, C_{14}-CH_3; and $CO_2CH_2\underline{CH_3}$). Anal. calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82; O, 9.74. Found: C, 80.22; H, 9.98; O, 9.80.

3. At -5°C, 0.46 g (1.4 mmol) of the preceding ester in 15 mL of toluene were reduced by 2.5 mL (2.8 mmol) of diisobutylaluminium hydride (DIBAL-H) in 5 mL of toluene. After quenching with an aqueous solution of 1 M NH_4Cl and the usual workup, the oily product (0.39 g) was purified by column chromatography (SiO_2, dichloromethane) to furnish the alcohol **3** as yellow oil (0.28 g, 70%).

IR (film cm^{-1}): 3363. ^{1}H NMR ($CDCl_3$): 6.36 (dd, 1H, $J = 15.0$, $J = 10.9$, C_{12}-H); 6.17 and 6.07 (2d, 2H, $J = 16.3$, C_7-H and C_8-H); 6.08 (d, 1H, $J = 10.9$, C_{13}-H); 5.81 (dt, 1H, $J = 15.0$, $J = 6.7$, C_{11}-H); 5.01 and 4.96 (2s, 2H, C_9-CH_2); 4.07 (s, 2H, C_{15}-H); 3.10 (d, 2H, $J = 6.7$, C_{10}-H); 2.01 (t, 2H, $J = 6.2$, C_4-H); 1.79 and 1.70 (2s, 6H, C_5-CH_3 and C_{14}-CH_3); 1.62 (m, 2H, C_3-H); 1.47 (m, 2H, C_2-H); 1.01 (s, 6H, C_1-CH_3). ^{13}C NMR ($CDCl_3$): 144.8, 137.4, 135.2, and 128.9 (C_1, C_5, C_9, and C_{14}); 134.4, 132.0, 127.7, 127.2, and 124.9 (C_7, C_8, C_{11}, C_{12}, and C_{13}); 114.8 (C_9-CH_2); 68.5 (C_{15}); 39.4, 35.7, 32.7, and 19.1 (C_4, C_3, C_2, and C_{10}); 34.1 (C_1); 28.7, 21.5, and 14.0 (C_5-CH_3, C_1-CH_3, and C_{14}-CH_3). Anal. calcd. for $C_{20}H_{30}O$: C, 83.86; H, 10.56; O, 5.59. Found: C, 83.59; H, 10.71; O, 5.70.

4. Alcohol **3** (0.25 g, 0.9 mmol) in 5 mL of pentane was oxidized by 0.78 g (9 mmol) of manganese dioxide in 5 mL of pentane at rt for 12 h. After purification of the oily product (0.22 g) by column chromatography (SiO_2, dichloromethane), the aldehyde **4** was obtained as yellow oil (0.17 g, 68%).

IR (film cm^{-1}): 1683, 1635. ^{1}H NMR ($CDCl_3$): 9.45 (s, 1H, C_{15}-H); 6.88 (d, 1H, $J = 11.2$, C_{13}-H); 6.63 (dd, 1H, $J = 15.1$, $J = 11.2$, C_{12}-H); 6.35 (dt, 1H, $J = 15.1$, $J = 6.7$, C_{11}-H); 6.15 and 6.08 (2d, 2H, $J = 16.6$, C_7-H and

C_8-H); 5.09 and 5.00 (2s, 2H, C_9-CH_2); 3.24 (d, 2H, $J = 6.7$, C_{10}-H); 2.01 (t, 2H, $J = 6.3$, C_4-H); 1.85 and 1.70 (2s, 6H, C_5-CH_3 and C_{14}-CH_3); 1.62 (m, 2H, C_3-H); 1.46 (m, 2H, C_2-H); 0.99 (s, 6H, C_1-CH_3). ^{13}C NMR ($CDCl_3$): 195.0 (C_{15}); 148.7, 142.7, 134.0, 128.3, and 126.9 (C_7, C_8, C_{11}, C_{12}, and C_{13}); 143.4, 137.2, 136.3, and 129.3 (C_6, C_5, C_9, and C_{14}); 115.8 (C_9-CH_2); 39.3, 36.2, 32.7, and 19.1 (C_4, C_3, C_2, and C_{10}); 34.1 (C_1); 28.7, 21.5, and 9.3 (C_5-CH_3, C_1-CH_3, and C_{14}-CH_3). Anal. calcd. for $C_{20}H_{28}O$: C, 84.45; H, 9.92; O, 5.62. Found: C, 84.21; H, 10.03; O, 5.76.

5. At 0°C, 3.5 g (15.6 mmol) of ethyl diethoxyphosphorylacetate in 20 mL of 1,2-dimethoxyethane (DME) were slowly added to a stirred suspension of 0.57 g of sodium hydride (14.2 mmol) in 20 mL of DME. After 1 h at 0°C, the solution was cooled to −5°C and 3.1 g (14.2 mmol) of **1** in 20 mL of DME were added, and the mixture was warmed to rt. The crude reaction was quenched with a aqueous solution of ammonium chloride. After extraction with ether and the usual workup, the crude product (3.9 g) was purified by column chromatography (SiO_2, dichloromethane 60/40) to give the ester **5** as yellow oil (2.46 g, 60%).

IR (film cm^{-1}): 1722. ^{1}H NMR ($CDCl_3$): 7.08 (dt, 1H, $J = 15.6$, $J = 6.6$, C_{11}-H); 6.11 and 6.06 (2d, 2H, $J = 16.5$, C_7-H and C_8-H); 5.91 (d, 1H, $J = 15.6$, C_{12}-H); 5.08 and 4.98 (2s, 2H, C_9-CH_2); 4.21 (q, 2H, $J = 7.1$, $CO_2\underline{CH_2}CH_3$); 3.18 (d, 2H, $J = 6.6$, C_{10}-H); 2.01 (t, 2H, $J = 6.3$, C_4-H); 1.70 (s, 3H, C_5-CH_3); 1.63 (m, 2H, C_3-H); 1.48 (m, 2H, C_2-H); 1.29 (t, 3H, $J = 7.1$, $CO_2CH_2\underline{CH_3}$); 1.00 (s, 6H, C_1-CH_3). ^{13}C NMR ($CDCl_3$): 166.4 (C_{13}); 146.6, 133.9, 128.3, and 122.5 (C_7, C_8, C_{11}, and C_{12}); 142.7, 137.2, and 129.2 (C_6, C_5, and C_9); 116.0 (C_9-CH_2); 60.1 ($CO_2\underline{CH_2}CH_3$); 39.3, 35.0, 32.7, and 19.1 (C_4, C_3, C_5, and C_{10}); 34.1 (C_1); 28.7, 21.5, and 14.1 (C_5-CH_3, C_1-CH_3, and $CO_2CH_2\underline{CH_3}$). Anal. calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78; O, 11.09. Found: C, 78.99; H, 9.98; O, 11.03.

6. Using the same procedure, starting from 1.5 g (6.9 mmol) of **1** and 1.34 (7.6 mmol) of diethyl cyanomethylphosphonate, the crude mixture (1.55 g) was purified by column chromatography (SiO_2, dichloromethane/cyclohexane 50/50) to provide 1.1 g (67%) of the nitrile **6**, as a mixture of two isomers 11*E* and 11*Z* (70/30).

11*E* isomer: IR (film cm^{-1}): 2221. ^{1}H NMR ($CDCl_3$): 6.85 (dt, 1H, $J = 16.3$, $J = 6.3$, C_{11}-H); 6.05 (s, 2H, C_7-H and C_8-H); 5.43 (d, 1H, $J = 16.3$, C_{12}-H); 5.13 and 4.98 (2s, 2H, C_9-CH_2); 3.20 (d, 2H, $J = 6.3$, C_{10}-H); 2.01 (t, 2H, $J = 6.4$, C_4-H); 1.68 (s, 3H, C_5-CH_3); 1.62 (m, 2H, C_3-H); 1.46 (m, 2H, C_2-H); 1.00 (s, 6H, C_1-CH_3). ^{13}C NMR ($CDCl_3$): 153.3, 133.3, 128.6, and 100.8 (C_7, C_8, C_{11}, and C_{12}); 141.4, 136.9, 129.7, and 117.3 (C_6, C_5, C_9, and C_{13}); 116.8 (C_9-CH_2); 39.2, 35.9, 32.7, and 19.1 (C_4, C_3, C_2, and C_{10}); 34.1 (C_1); 28.7 and 21.5 (C_5-CH_3 and C_1-CH_3). Anal. calcd. for $C_{17}H_{23}N$: C, 84.59; H, 9.60; N, 5.80. Found: C, 84.32; H, 9.88; N, 5.80.

11*Z* isomer: IR (film cm^{-1}): 2220. ^{1}H NMR ($CDCl_3$): 6.58 (dt, 1H, $J = 10.9$, $J = 7.4$, C_{11}-H); 6.16 and 6.07 (2d, 2H, $J = 17.0$, C_7-H and C_8-H); 5.45 (d, 1H, $J = 10.9$, C_{12}-H); 5.08 and 5.00 (2s, 2H, C_9-CH_2); 3.40 (d, 2H,

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$J = 7.4$, C_{10}-H); 2.02 (t, 2H, $J = 6.2$, C_4-H); 1.70 (s, 3H, C_5-CH_3); 1.63 (m, 2H, C_3-H); 1.48 (m, 2H, C_2-H); 1.02 (s, 6H, C_1-CH_3). ^{13}C NMR ($CDCl_3$): 152.9, 133.7, 128.3, and 100.2 (C_7, C_8, C_{11}, and C_{12}); 142.0, 137.0, 129.6, and 115.7 (C_6, C_5, C_9, and C_{13}); 116.0 (C_9-CH_2); 39.3, 34.7, 32.8, and 19.1 (C_4, C_3, C_2, and C_{10}); 34.1 (C_1); 28.7 and 21.5 (C_5-CH_3 and C_1-CH_3). Anal. calcd. for $C_{17}H_{23}N$: C, 84.59; H, 9.60; N, 5.80. Found: C, 84.34; H, 9.81; N, 5.85.

7. Analogously, at -10°C, with 6 g (27.5 mmol) of **1** and 5.88 g (27.5 mmol) of diethyl 2-oxopropylphosphonate, the crude mixture (7.1 g) was purified by column chromatography (SiO_2, dichloromethane) to give the ketone **7** as yellow oil (3.52 g, 51%). A more polar fraction was constituted by the compound **8** as yellow oil (0.85 g, 13%).

IR (film cm^{-1}): 1674, 1699, 1625. ^{1}H NMR (DMSO D-6): 6.91 (dt, 1H, $J = 16.0$, $J = 6.4$, C_{11}-H); 6.12 and 6.05 (2d, 2H, $J = 16.3$, C_7-H and C_8-H); 6.08 (d, 1H, $J = 16.0$, C_{12}-H); 5.12 and 5.03 (2s, 2H, C_9-CH_2); 3.22 (d, 2H, $J = 6.4$, C_{10}-H); 2.19 (s, 3H, C_{14}-H); 1.97 (t, 2H, $J = 6.0$, C_4-H); 1.64 (s, 3H, C_5-CH_3); 1.56 (m, 2H, C_3-H); 1.42 (m, 2H, C_2-H); 0.95 (s, 6H, C_1-CH_3). ^{13}C NMR ($CDCl_3$): 198.3 (C_{13}); 145.9 (C_{11}); 142.7, 137.1, and 129.4 (C_6, C_5, and C_9); 133.8 and 128.4 (C_7 and C_8); 132.2 (C_{12}); 116.1 (C_9-CH_2); 39.3 (C_2); 35.3 (C_{10}); 34.7 (C_1); 32.7 (C_4); 28.7 (C_1-CH_3); 26.8 (C_{14}); 21.5 (C_5-CH_3); 19.1 (C_3). Anal. calcd. for $C_{18}H_{26}O$: C, 83.67; H, 10.14; O, 6.19 found: C, 83.42; H, 10.28; N, 6.30.

8. IR (film cm^{-1}): 3445, 1672, 1621. ^{1}H NMR ($CDCl_3$): 7.08 (dd, 1H, $J = 16.0$, $J = 8.0$, C_{11}-H); 6.20 (d, 1H, $J = 16.0$, C_{12}-H); 6.25, 6.12, 6.02, and 6.01 (4d, 4H, $J = 16.4$, $C_{8'}$-H, $C_{7'}$-H, C_8-H, and C_7-H); 5.24, 5.12, 5.07, and 5.03 (4s, 4H, C_9-CH_2, and $C_{9'}$-CH_2); 4.01 (m, 1H, C_{11}-H); 3.37 (dd, 1H, $J = 8.0$, C_{10}-H); 2.73 (dd, 1H, $J = 13.8$, $J = 3.2$, C_{10}-H); 2.30 (s, 3H, C_{13}-CH_3); 2.21 (dd, 1H, $J = 13.8$, $J = 9.3$, C_{10}-H); 2.00 (t, 4H, $J = 6.2$, $C_{4,4'}$-H); 1.66 (s, 6H, $C_{5,5'}$-CH_3); 1.60 (m, 4H, $C_{3,3'}$-H); 1.45 (m, 4H, $C_{2,2'}$-H); 0.99, 0.98, and 0.97 (3s, 12H, $C_{1,1'}$-CH_3). ^{13}C NMR ($CDCl_3$): 198.5 (CO); 147.0 (C_{11}); 145.4, 142.6, 137.1, 137.0, 129.7, and 129.4 ($C_{9'}$, C_6, $C_{6'}$, and C_5); 134.0, 133.8, 128.3, and 128.1 ($C_{8'}$, $C_{7'}$, C_8, and C_7); 132.3 (C_{12}); 117.0 and 115.7 ($C_{9'}$-CH_2 and C_9-CH_2); 70.9 (C_{11}); 49.9 (C_{10}); 39.2 ($C_{2,2'}$); 38.5 ($C_{10'}$); 34.0 ($C_{1,1'}$); 32.7 ($C_{4,4'}$); 28.7 ($C_{1,1'}$-CH_3); 26.9 (C_{13}-CH_3); 21.5 ($C_{5,5'}$-CH_3); 19.1 ($C_{3,3'}$). Anal. calcd. for $C_{33}H_{48}O_2$: C, 83.14; H, 10.15; O, 6.71. Found: C, 82.99; H, 10.23; N, 6.78.

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