Synthesis of 9-Methylene Analogs of Retinol, Retinal, Retinonitrile and Retinoic Acid

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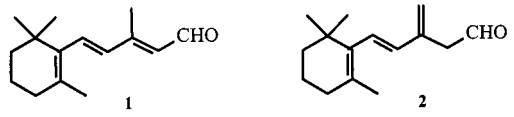
Retinoids, 9-methylene analogs of retinol, retinal, retinonitrile and retinoic acid, were synthesised from a new synthon β-methylenealdehyde.

Introduction

Natural retinoids play important roles in vision and diverse cellular process such as cell differentiation, proliferation, apoptosis and developmental changes. Moreover, these compounds act as modulators for inflammatory and immunological events. Natural and synthetic retinoids are widely used in the treatment of acute promyelocytic leukemia (APL), cancers and a variety of cutaneous malignancies.[1−3] Retinoic acid receptors are divided into two classes: the 9-*cis* retinoic acid receptor (retinoic X receptor, RXR) and all-*trans* retinoic acid receptor (RAR). Recently the three-dimensional structure of a RXR-RAR DNA-binding complex was determined.[4]

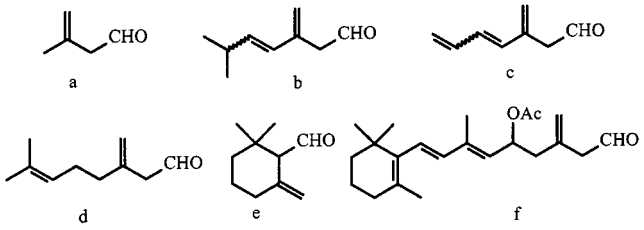
Thus, the synthesis of novel retinoid analogues appeared important in order to obtain more specific products suitable for therapeutic applications. Consequently we developed a synthesis of 9-methylene analogs of natural retinoids in which conjugation of the double bonds is broken at the C_9-C_{10} position.

All the methodologies for synthesizing the polyethylenic side-chain of retinoids were reviewed and, among these, β-ionylideneacetaldehyde **1** [3-methyl-5-(2,6,6-trimethyl-cyclohex-1-enyl)-penta-2,4-dienal] was widely used as a key intermediate, especially by French teams (Scheme 1).[5,6]



Scheme 1

The use of β-methylenealdehyde **2** [3-methylene-5-(2,6,6-trimethyl-cyclohex-1-enyl)-pent-4-enal] as an alternative to β-ionylideneacetaldehyde has been reported in a synthesis of 13*E* and 13*Z* retinoic acids.[7−9] In these example the β-methylene stereochemistry could be kept and thus we decided to synthesize 9-methylene analogs of retinol, retinal, retinonitrile and retinoic acid. It should be noted here that only a few examples of β-methylenealdehydes in organic chemistry have been reported (Scheme 2).[10] These examples deal with terpene chemistry, and one of them (methylenealdehyde, f) was used as an intermediate for retinal synthesis.[10f]



Scheme 2

The synthon **2** was synthesized from β-ionone **3** by formylation ($CH_3ONa/HCOOCH_3$/pentane); acetalization of the sodium salts of the hydroxymethylenic compounds **4** (CH_3OH/H_2SO_4) furnished the β-ketoacetal **5**. A Wittig reaction (tBuOK/$(C_6H_5)_3PCH_3$ Br^-/cyclohexane) and mild acidic hydrolysis of the β-methyleneacetal **6** (HCOOH/pentane) produced the β-methylenealdehyde **2** (35% from **3**) with no detectable conjugated isomers (Scheme 3).

Starting from β-methylenealdehyde **2**, the side-chain of the retinoids **8** and **11** was built by a Horner−Emmons reaction with a C-5 unit (Scheme 4). When the anion derived from ethyl 4-(diethoxyphosphoryl)-3-methylbut-2-enoate (2*E*/2*Z* = 50:50) reacted with **2** (NaH, −5 °C, 15 min. then **2**, −60 °C), the corresponding ester **7** was formed as a mixture of 13*E*/13*Z* (50:50) isomers (55%). Saponification of **7** (0.75 M ethanolic NaOH, reflux 3 h) led to the acid **8** (13*E*/13*Z*: 50:50) in 55% yield. The retinol analogue **11** was obtained by DIBAL-H reduction of ethyl ester **7** (DIBAL-H, −78 °C, then room temp., 30 min.) as a mixture of 13*E*/13*Z* (65:35) isomers (75% yield).

Similarly, the C-5 anion of ethyl 3-cyano-2-methylprop-2-enyl-phosphonate (2*E*/2*Z* = 65:35), afforded the nitrile **9** (Scheme 4) as a mixture of 13*E*/13*Z* (65:35) isomers (50%

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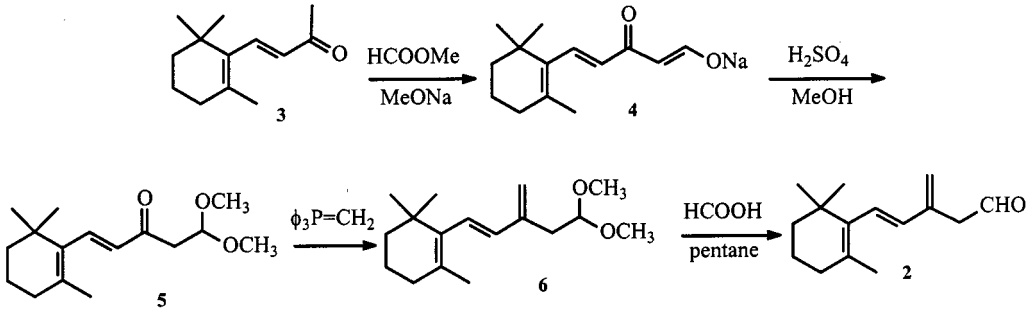
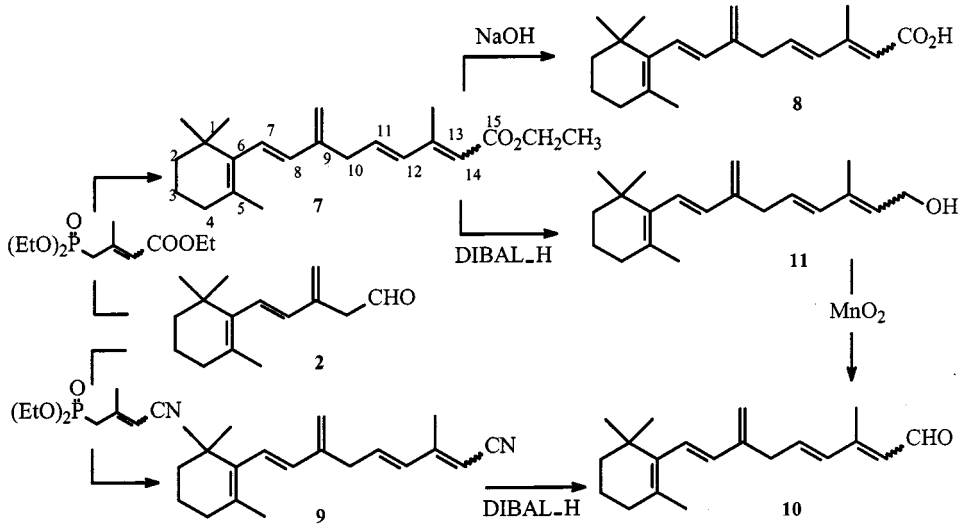


Scheme 3



Scheme 4

yield). The retinal analogue **10** was obtained by DIBAL-H reduction of nitrile **9** (DIBAL-H, −78 °C, then room temp., 30 min.) as a mixture of 13*E*/13*Z* (65:35) isomers (70% yield). The retinol analogue **11** could be obtained by oxidation of the alcohol **11** (MnO_2, room temp., 3 h) with a yield of 75% (Scheme 3).

The new 9-methylene analogs of retinol, retinal, retinonitrile and retinoic acid are obtained with no detectable amounts of conjugated isomers.

Experimental Section

General: All chemicals were purchased from Sigma-Aldrich. Melting points were measured on a Leitz 350 heated stage microscope and are not corrected. IR spectra were recorded on a Bruker IFS 55 spectrometer. ^1H and ^{13}C NMR spectra were determined on a Bruker Avance DPX 400 spectrometer (^1H, 400 MHz, ^{13}C, 100 MHz). Chemicals shifts (δ) are expressed in ppm downfield from internal TMS. *J* values are in Hertz. A pure analytical sample of the *E* and *Z* isomers of compounds **7**−**11** was obtained by analytical TLC, performed on Merck silica gel (60 F_{254}) plates. Elemental analyses were within ±0.3% of theoretical values. The traditional retinoid numbering system[11,12] is used for spectroscopic data (Scheme 4). The Chemical Abstracts nomenclature is used below.

Ethyl 3-Methyl-7-methylene-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,8-trienoate (7): Ethyl 4-(diethoxyphosphoryl)-3-methyl-but-2-enoate (2*E*/2*Z*, 50:50; 10.1 g, 38 mmol) was dissolved in DME (50 mL) and added, at −10 °C, to a suspension of of NaH (60% dispersion in mineral oil; 1.4 g, 35 mmol) in DME (15 mL). The solution was stirred for 15 min. and aldehyde **2**[7−9] (7.6 g, 35 mmol) in DME (50 mL) was slowly added at −60 °C. The mixture was then warmed to room temp. and hydrolysed with an aqueous saturated NH_4Cl solution. The aqueous layer was extracted with Et_2O and the organic layers were washed with H_2O and dried ($MgSO_4$). The residue was purified by chromatography on silica gel with CH_2Cl_2/cyclohexane (70:30) to provide the esters **7** (13*E*/13*Z* = 50:50) as a yellow oil (6.29 g, 55%).

7 (13*E*): IR (film): $\tilde{\nu}$ = 1708, 1613 cm^{-1}. − ^1H NMR ([D_6]DMSO): δ = 6.30 (d, *J* = 15.7, 1 H, C_{12}-H), 6.22 (dt, *J* = 15.7, *J′* = 6.2, 1 H, C_{11}-H), 6.14 and 6.04 (2d, *J* = 16.4, 2 H, C_7-H and C_8-H), 5.74 (s, 1 H, C_{14}-H), 5.07 and 4.99 (2s, 2 H, C_9=CH_2), 4.08 (q, *J* = 7.1, 2 H, $CO_2CH_2CH_3$), 3.15 (d, *J* = 6.2, 2 H, C_{10}-H), 2.20 (s, 3 H, C_{13}-CH_3), 1.97 (m, 2 H, C_4-H), 1.64 (s, 3 H, C_5−CH_3), 1.56 (m, 2 H, C_3-H), 1.41 (m, 2 H, C_2-H), 1.20 (t, *J* = 7.1, 3 H, $CO_2CH_2CH_3$), 0.95 (s, 6 H, C_1-CH_3). − ^{13}C NMR: δ = 166.6 (C_{15}), 152.3, 144.1, 137.4 and 128.9 (C_6, C_5, C_9 and C_{13}), 135.6 (C_{11}), 134.8 (C_{12}), 134.4 and 128.1 (C_7 and C_8), 117.9 (C_{14}), 116.4 (C_9-CH_2), 59.6 ($CO_2CH_2CH_3$), 39.3 (C_2), 35.7 (C_{10}), 34.1 (C_1), 32.6 (C_4), 28.9 (C_1-CH_3), 21.7 (C_2-CH_3), 19.1 (C_4), 14.5 ($CO_2CH_2CH_3$), 13.8 (C_{13}-CH_3).

7 (13*Z*): IR (film): $\tilde{\nu}$ = 1714, 1603 cm^{-1}. − ^1H NMR ([D_6]DMSO): δ = 7.57 (d, *J* = 15.9, 1 H, C_{12}-H), 6.25 (dt, *J* = 15.9, *J′* = 6.6, 1 H, C_{11}-H), 6.13 and 6.03 (2d, *J* = 16.4, 2 H, C_7-H and C_8-H), 5.66 (s, 1 H, H_{14}), 5.08 and 5.01 (2s, 2 H, C_9=CH_2), 4.06 (q, *J* = 7.1, 2 H, $CO_2CH_2CH_3$), 3.17 (d, *J* = 6.6, 2 H, C_{10}-H), 1.98 (m, 5 H, C_{13}-

CH_3 and C_4-H), 1.64 (s, 3 H, C_5-CH_3), 1.56 (m, 2 H, C_3-H), 1.41 (m, 2 H, C_2-H), 1.19 (t, J = 7.1, 3 H, $CO_2CH_2CH_3$), 0.94 (s, 6 H, C_1-CH_3). – ^{13}C NMR: δ = 165.6 (C_{15}), 150.9, 144.1, 137.4 and 128.8 (C_6, C_5, C_9 and C_{13}), 137.1 (C_{11}), 134.3 and 128.2 (C_7 and C_8), 128.7 (C_{12}), 116.5 (C_9-CH_2), 116.2 (C_{14}), 59.5 ($CO_2CH_2CH_3$), 39.3 (C_2), 36.2 (C_{10}), 34.1 (C_1), 32.6 (C_4), 28.9 (C_1-CH_3), 21.7 (C_2-CH_3), 20.8 (C_{13}–CH_3), 19.1 (C_4), 14.5 ($CO_2CH_2CH_3$).

3-Methyl-7-methylene-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,8-trienoic Acid (8): A solution of the esters **7** (1.9 g, 5.8 mmol) in ethanolic 0.75 M NaOH (50 mL) was refluxed for 3 h. H_2O (50 mL) was then added at 0 °C and the solution was acidified with cold 10% HCl. The mixture was extracted with ether and the combined organic layers were washed with water and dried ($MgSO_4$). Removal of the solvent by rotary evaporation provided a brown oil, which was purified by column chromatography on silica gel (CH_2Cl_2/CH_3OH, 98:2) to furnish the acids **8** (13*E*/13*Z* = 50:50) as an orange oil (1.83 g, 54%).

8 (13*E*): IR (film): ṽ = 1685, 1608 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 6.30 (dt, J = 15.7, J' = 6.0, 1 H, C_{11}-H), 6.23 (d, J = 15.7, 1 H, C_{12}-H), 6.15 and 6.06 (2d, J = 16.4, 2 H, C_7-H and C_8-H), 5.75 (s, 1 H, C_{14}-H), 5.05 and 4.98 (2s, 2 H, C_9=CH_2), 3.18 (d, J = 6.0, 2 H, C_{10}-H), 2.31 (s, 3 H, C_{13}-CH_3), 2.03 (m, 2 H, C_4-H), 1.70 (s, 3 H, C_5-CH_3), 1.61 (m, 2 H, C_3-H), 1.46 (m, 2 H, C_2-H), 1.01 (s, 6 H, C_1-CH_3). – ^{13}C NMR: δ = 172.6 (C_{15}), 154.8, 143.9, 137.2 and 129.1 (C_6, C_5, C_9 and C_{13}), 135.9 (C_{11}), 134.7 (C_{12}), 134.1 and 128.2 (C_7 and C_8), 117.3 (C_{14}), 115.4 (C_9-CH_2), 39.3 (C_2), 35.9 (C_{10}), 34.1 (C_1), 32.7 (C_4), 28.7 (C_1-CH_3), 21.5 (C_5-CH_3), 19.1 (C_3), 13.9 (C_{13}-CH_3).

8 (13*Z*): IR (film): ṽ = 1683, 1600 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 7.69 (d, J = 15.8, 1 H, C_{12}-H), 6.28 (dt, J = 15.8, J' = 6.9, 1 H, C_{11}-H), 6.19 and 6.08 (2d, J = 16.7, 2 H, C_7-H and C_8-H), 5.68 (s, 1 H, C_{14}-H), 5.04 and 4.89 (2s, 2 H, C_9=CH_2), 3.23 (d, J = 6.9, 2 H, C_{10}-H), 2.06 (s, 3 H, C_{13}-CH_3), 2.10 (m, 2 H, C_4-H), 1.71 (s, 3 H, C_5-CH_3), 1.61 (m, 2 H, C_3-H), 1.46 (m, 2 H, C_2-H), 1.01 (s, 6 H, C_1-CH_3). – ^{13}C NMR: δ = 171.9 (C_{15}), 153.3, 144.2, 137.3 and 129.0 (C_6, C_5, C_9 and C_{13}), 137.6 (C_{11}), 134.2 and 128.2 (C_7 and C_8), 128.9 (C_{12}), 115.6 (C_{14}), 115.1 (C_9-CH_2), 39.3 (C_2), 36.3 (C_{10}), 34.1 (C_1), 32.7 (C_4), 28.7 (C_1-CH_3), 21.3 (C_5-CH_3), 21.2 (C_{13}-CH_3), 19.2 (C_4). – MS: *m*/*z* (%) = 300 (100) [M$^+$], 111 (97). – HRMS ($C_{20}H_{28}O_2$): calcd. 300.2089; found 300.2092.

3-Methyl-7-methylene-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,8-trienenitrile (9): Ethyl 3-cyano-2-methylprop-2-enyl-phosphonate (2*E*/2*Z* = 65:35; 3.63 g, 16.7 mmol) was dissolved in DME (20 mL) and added at 0 °C, under argon, to a suspension of NaH (60% dispersion in mineral oil; 0.61 g, 15.2 mmol) in DME (10 mL). The solution was stirred for 15 min. and aldehyde **1** (3.31 g, 15.2 mmol) in 30 mL of DME was slowly added at −60 °C. The mixture was then warmed to room temp. and hydrolysed with aq. satd. NH_4Cl solution. The aqueous layer was extracted with Et_2O and the organic layers were washed with H_2O and dried ($MgSO_4$).The residue was purified by chromatography on silica gel with CH_2Cl_2/cyclohexane (70:30) to provide the nitriles **9** (13*E*/13*Z* = 65:35) as a yellow oil (4.05 g, 50%).

9 (13*E*): IR (film): ṽ = 2213 cm^{-1}. – ^{1}H NMR (D_6]DMSO): δ = 6.35 (d, J = 15.7, 1 H, C_{12}-H), 6.27 (dt, J = 15.7, J' = 6.2, 1 H, C_{11}-H), 6.12 and 6.04 (2d, J = 16.5, 1 H, C_7-H and C_8-H), 5.56 (s, 1 H, C_{14}-H), 5.09 and 5.01 (2s, 2 H, C_9=CH_2), 3.16 (d, J = 6.2, 2 H, C_{10}-H), 2.08 (s, 3 H, C_{13}-CH_3), 1.98 (m, 2 H, C_4-H), 1.64 (s, 3 H, C_5-CH_3), 1.57 (m, 2 H, C_3-H), 1.42 (m, 2 H, C_2-H), 0.95 (s, 6 H, C_1-CH_3). – ^{13}C NMR: δ = 156.8, 143.5, 137.2 and 129.3 (C_6, C_5, C_9 and C_{13}), 137.0, 133.9, 131.6 and 128.4 (C_7, C_8, C_{11} and C_{12}), 117.7 (C_{15}), 115.7 (C_9-CH_2), 96.5 (C_{14}), 39.3, 35.8, 32.7 and 19.4 (C_4, C_3, C_2 and C_{10}), 34.1 (C_1), 28.7, 21.4 and 16.6 (C_5-CH_3, C_1-CH_3 and C_{13}-CH_3).

9 (13*Z*): IR (film): ṽ = 2213 cm^{-1}. – ^{1}H NMR (D_6]DMSO): δ = 6.62 (d, J = 15.5, 1 H, C_{12}-H), 6.35 (dt, J = 15.5, J' = 6.5, 1 H, C_{11}-H), 6.13 and 6.05 (2d, J = 16.4, 2 H, C_7-H and C_8-H), 5.51 (s, 1 H, C_{14}-H), 5.11 and 5.04 (2s, 2 H, C_9=CH_2), 3.24 (d, J = 6.5, 2 H, C_{10}-H), 1.97 (m, 5 H, C_{13}-CH_3 and C_4-H), 1.65 (s, 3 H, C_5-CH_3), 1.56 (m, 2 H, C_3-H), 1.41 (m, 2 H, C_2-H), 0.95 (s, 6 H, C_1-CH_3). – ^{13}C NMR: δ = 156.6, 143.7, 137.3 and 128.9 (C_6, C_5, C_9 and C_{13}), 138.7, 134.2, 128.7 and 128.3 (C_7, C_8, C_{11}, and C_{12}), 117.3 (C_{15}), 116.8 (C_9–CH_2), 95.6 (C_{14}), 39.3, 35.5, 32.6 and 19.1 (C_4, C_3, C_2 and C_{10}), 34.1 (C_1), 28.9, 21.7 and 19.2 (C_5-CH_3, C_1-CH_3 and C_{13}-CH_3).

3-Methyl-7-methylene-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,8-trienal (10): DIBAL-H (20% in toluene; 6.3 mL, 7.5 mmol) was added slowly at −78 °C to nitrile **9** (2.11 g, 7.5 mmol) in toluene (10 mL). After stirring for 30 min., the reaction mixture was quenched with aq. satd. NH_4Cl solution. The resulting crude product was washed with ether and the aqueous layer extracted with Et_2O. The organic layers were extracted with H_2O and dried ($MgSO_4$). The combined extracts were concentrated and the oily product was purified by chromatography on silica gel eluting with CH_2Cl_2/CH_3OH (98:2) to provide the aldehydes **10** (13*E*/13*Z* = 65:35) as a yellow oil (1.5 g, 70%).

10 (13*E*): IR (film): ṽ = 1668, 1632 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 10.13 (d, J = 8.0, 1 H, C_{15}-H), 6.40 (dt, J = 15.7, J' = 6.4, 1 H, C_{11}-H), 6.30 (d, J = 15.7, 1 H, C_{12}-H), 6.14 and 6.07 (2d, J = 16.3, 2 H, C_7-H and C_8-H), 5.92 (d, J = 8.0, 1 H, C_{14}-H), 5.06 and 4.98 (2s, 2 H, C_9=CH_2), 3.20 (d, J = 6.4, 2 H, C_{10}-H), 2.28 (s, 3 H, C_{13}-CH_3), 2.00 (m, 2 H, C_4-H), 1.70 (s, 3 H, C_5-CH_3), 1.62 (m, 2 H, C_3-H), 1.46 (m, 2 H, C_2-H), 0.99 (s, 6 H, C_1-CH_3). – ^{13}C NMR: δ = 191.4 (C_{15}), 154.4, 143.6, 137.1 and 129.2 (C_6, C_5, C_9 and C_{13}), 136.9 (C_{11}), 134.5 (C_{12}), 134.0 and 128.3 (C_7 and C_8), 128.6 (C_{14}), 115.6 (C_9–CH_2), 39.3 (C_2), 36.0 (C_{10}), 34.1 (C_1), 32.7 (C_4), 28.7 (C_1-CH_3), 21.5 (C_5-CH_3), 19.1 (C_3), 12.9 (C_{13}-CH_3).

10 (13Z): IR (film): ṽ = 1669, 1633 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 10.19 (d, J = 8.1, 1 H, C_{15}-H), 7.18 (d, J = 15.5, 1 H, C_{12}-H), 6.30 (dt, J = 15.5, J' = 6.6, 1 H, C_{11}-H), 6.15 and 6.08 (2d, J = 16.3, 2 H, C_7-H and C_8-H), 5.85 (d, J = 8.1, 1 H, C_{14}-H), 5.08 and 5.00 (2s, 2 H, C_9=CH_2), 3.24 (d, J = 6.6, 2 H, C_{10}-H), 2.09 (s, 3 H, C_{13}-CH_3), 2.01 (m, 2 H, C_4-H), 1.70 (s, 3 H, C_5-CH_3), 1.62 (m, 2 H, C_3-H), 1.46 (m, 2 H, C_2-H), 0.99 (s, 6 H, C_1-CH_3). – ^{13}C NMR: δ = 190.1 (C_{15}), 154.5, 143.6, 137.1 and 129.3 (C_6, C_5, C_9 and C_{13}), 137.9 (C_{11}), 133.9 and 128.3 (C_7 and C_8), 127.6 (C_{14}), 126.4 (C_{12}), 115.7 (C_9-CH_2), 39.2 (C_2), 36.2 (C_{10}), 34.1 (C_1), 32.7 (C_4), 28.7 (C_1-CH_3), 21.4 (C_5-CH_3), 21.2 (C_{13}-CH_3), 19.1 (C_3). – MS: *m*/*z* (%) = 284 (47) [M$^+$], 95 (100). – HRMS ($C_{20}H_{28}O$): calcd. 284.2140; found 284.2139.

3-Methyl-7-methylene-9-(2,6,6-trimethyl-cyclohex-1-enyl)-nona-2,4,8-trienol (11): DIBAL-H (20% in toluene; 9.2 mL, 11 mmol) was added slowly at −5 °C to ester **7** (1.8 g, 5.5 mmol) in toluene (10 mL). After stirring for 30 min. at −5 °C, the reaction mixture was quenched with aq. satd. NH_4Cl solution. The resulting crude product was washed with ether and the aqueous layer extracted with Et_2O. The organic layers were extracted with H_2O and dried ($MgSO_4$). The combined extracts were concentrated and the oily product was purified by chromatography on silica gel, eluting with CH_2Cl_2/CH_3OH (98:2) to provide the alcohol **11** (13*E*/13*Z* = 65:35) as a yellow oil (1.44 g, 71%).

11 (13*E*): IR (film): ṽ = 3329 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 6.17 (2d, J = 16.0, 2 H, C_7-H and C_{12}-H), 6.06 (d, J = 16.0, 1 H, C_8-H), 5.81 (dt, J = 16.0, J' = 6.7, 1 H, C_{11}-H), 5.61 (t, J = 6.3,

1 H, C_{14}-H), 5.00 and 4.97 (2s, 2 H, C_9=CH_2), 4.30 and 4.28 (2d, J = 6.3, 1 H, C_{15}-H), 3.10 (d, J = 6.7, 2 H, C_{10}-H), 2.01 (m, 2 H, C_4-H), 1.81 (s, 3 H, C_{13}-CH_3), 1.70 (s, 3 H, C_5-CH_3), 1.62 (m, 2 H, C_3-H), 1.47 (m, 2 H, C_2-H), 1.00 (s, 6 H, C_1-CH_3). − ^{13}C NMR: δ = 144.9, 137.4, 136.3, and 128.9 (C_6, C_5, C_9 and C_{13}), 135.3, 134.4, 127.9 and 127.8 (C_7, C_8, C_{11} and C_{12}), 128.1 (C_{14}), 114.7 (C_9-CH_2), 59.3 (C_{15}), 39.4 (C_2), 35.6 (C_{10}), 34.1 (C_1), 32.7 (C_4), 28.7 (C_1-CH_3), 21.5 (C_5-CH_3), 19.1 (C_3), 12.5 (C_{13}-CH_3).

11 (13*Z*): IR (film): $\tilde{\nu}$ = 3346 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 6.53 (d, J = 15.5, 1 H, C_{12}-H), 6.17 and 6.06 (2d, J = 16.3, 2 H, C_7-H and C_8-H), 5.90 (dt, J = 15.5, J' = 6.7, 1 H, C_{11}-H), 5.52 (t, J = 7.0, 1 H, C_{14}-H), 5.02 and 4.97 (2s, 2 H, C_9=CH_2), 4.30 (d, J = 7.0, 2 H, C_{15}-H), 3.14 (d, J = 6.7, 2 H, C_{10}-H), 2.01 (m, 2 H, C_4-H), 1.88 (s, 3 H, C_{13}-CH_3), 1.70 (s, 3 H, C_5-CH_3), 1.62 (m, 2 H, C_3-H), 1.47 (m, 2 H, C_2-H_2), 1.00 (s, 6 H, C_1-CH_3). − ^{13}C NMR: δ = 144.7, 137.4, 135.3 and 128.9 (C_6, C_5, C_9 and C_{13}), 134.3 and 127.9 (C_7 and C_8), 130.3 (C_{11}), 127.6 (C_{12}), 126.6 (C_{14}), 114.9 (C_9−CH_2), 58.3 (C_{15}), 39.3 (C_2), 36.0 (C_{10}), 34.1 (C_1), 32.7 (C_4), 28.7 (C_1-CH_3), 21.5 (C_5-CH_3), 20.5 (C_{13}-CH_3), 19.1 (C_3). − MS: m/z (%) = 286 (42) [M^+], 268 (100). − HRMS ($C_{20}H_{30}O$): calcd. 286.2296; found 286.2294.

Aldehydes 10: Alcohols **11** (4.77 g, 16.7 mmol) and MnO_2 (14.53 g, 167 mmol) in 80 mL of pentane were stirred at room temp. for 3 h. After filtration, the organic layer was concentrated and the oily product was purified by chromatography on silica gel with CH_2Cl_2 to provide the aldehydes **10** (13*E*/13*Z* = 65:35) as a yellow oil (3.37 g, 71%).

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