Supporting Information

Stereoselective Synthesis of Annular 9-cis-Retinoids and Binding Characterization to the Retinoid X Receptor

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Table of contents

S2-S7: Experimental Procedures for the synthesis of 7a,c,d; 8a,c,d, 9a,c,d and 3a,c,d; and Spectroscopic Characterization of all compounds described in the manuscript.

S8: Figure S1. Histogram of torsional values available to analogs 3a-3d.

S9-S40: Copies of 1H and 13C-NMR spectra
2-{(1E,3E)-5-Hydroxy-3-methylpenta-1,3-dien-1-yl}cyclopent-1-en-carbaldehyde 7a. General Procedure: To a solution of β-bromoaldehyde 5a (154 mg, 0.88 mmol) in NMP (7 mL) were added AsPh 3 (12.5 mg, 0.04 mmol) and Pd 2dba 3 (37.3 mg, 0.04 mmol). After stirring at room temperature for 10 min, a solution of vinylstannane 6 (459 mg, 1.18 mmol) in NMP (4 mL) was added, and the reaction mixture was stirred at room temperature for 5 min. The reaction was quenched by addition of a saturated aqueous KF solution (5 mL) and stirring was maintained for 30 min. The aqueous layer was extracted with ether (3x) and the combined organic layers were washed with saturated KF (3x) and H 2O (3x), dried (MgSO 4), filtered and concentrated. The residue was purified by chromatography (silica, 70:30 hexane/ethyl acetate) to yield 160 mg (95%) of 7a as an oil. 1H NMR (CDCl 3, 250.13 MHz) δ 1.85 (3H, C3'-CH 3), 1.8-1.9 (2H, m, 2H4), 2.64 (2H, t, J = 7.3 Hz, 2H3), 2.78 (2H, t, J = 7.5 Hz, 2H5), 4.34 (2H, d, J = 6.5 Hz, 2H5'), 5.87 (1H, t, J = 6.5 Hz, H4'), 6.53 (1H, d, J = 15.6 Hz, H1'), 7.09 (1H, d, J = 15.6 Hz, H2'), 10.24 (1H, s, CHO); 13C NMR (CDCl 3, 62.89 MHz) δ 12.5 (q), 21.2 (t), 31.0 (t), 34.7 (t), 59.5 (t), 119.5 (d), 135.1 (d), 135.7 (s), 139.4 (s), 140.7 (d), 158.0 (d, C=O); IR (CH 2Cl2) υ 3500-3100 (broad, OH), 2952 (m, C-H), 2850 (m, C-H), 1648 (s, C=O), 1600 (s, C=C), 1370 (m), 1213 (m), 1013 (m), 957 (m) cm -1; UV (MeOH) λ max 252, 314, 326 nm; MS m/z (%) 192 (M+, 27), 174 (M+-H2O, 13), 161 (12), 147 (11), 145 (14), 133 (61), 131 (23), 121 (100), 117 (17), 115 (15), 108 (34), 105 (39), 93 (14), 91 (36), 79 (21), 77 (21); HRMS [M+] calcd. for C12H16O2, 192.1151; found, 192.1153.

(2E,4E)-3-Methyl-5-{2-{[(E)-2-(2,6,6-trimethylcyclohex-1-en-1-yl)ethenyl]-1-cyclopenten-1-yl}-2,4-pentadien-1-ol 8a. General Procedure: To a cooled (-30 °C) suspension of phosphonium salt 4 (2.32 g, 4.84 mmol) in THF (10 mL) was added n-BuLi (3.93 mL, 1.23 M in THF, 4.84 mmol) and the resulting solution was stirred at 0 °C for 1 h. Aldehyde 7a (0.3 g, 1.56 mmol) in THF (7 mL) was then added via cannula at -78 °C, and the reaction mixture was stirred at -78 °C for 1 h and at 25 °C for 2 h. Water was added, and the aqueous layer was extracted with ether (3x). The combined organic layers were washed with H2O (3x) and brine, dried (MgSO 4), and concentrated. Purification by chromatography (silica, 80:20 hexane/ethyl acetate) afforded 0.27 g (55%) of alcohol 8a as an oil. 1H NMR (CDCl 3, 400.13 MHz) δ 1.03 (6H, s, C6'-2CH 3), 1.4-1.5 (2H, m, 2H5'), 1.6-1.7 (4H, m, 2 X CH 2), 1.75 (3H, s, C2'-2CH 3), 1.87 (3H, s, C3'-CH 3), 2.03 (2H, t, J = 6.0 Hz, 2H3'), 2.6-2.7 (4H, m, 2 X CH 2), 4.30 (2H, d, J = 6.9 Hz, 2H1), 5.71 (1H, t, J = 6.9 Hz, H2), 6.09 (1H, d, J = 15.7 Hz, H2'), 6.21 (1H, d, J = 15.7 Hz), 6.56 (1H, t, J = 15.7 Hz), 6.75 (1H, t, J = 15.7 Hz); 13C NMR (CDCl 3, 100.61 MHz) δ 12.6 (q), 19.2 (t), 21.3 (t), 21.8 (q), 28.9 (q, 2x), 33.0 (t), 33.5 (t), 33.6 (t), 34.1 (s), 39.4 (t), 59.4 (t), 122.0 (d), 126.8 (d), 128.7 (d), 129.3 (s), 129.8 (d), 133.0
(2E,4E)-3-Methyl-5-[2-[(E)-2-(2,6,6-trimethylcyclohex-1-en-1-yl)ethenyl]-1-cyclopenten-1-yl}-2,4-pentadienal 9a. **General Procedure**: To a mixture of alcohol 8a (0.2 g, 0.64 mmol) in CH2Cl2 (17 mL) was added MnO2 (1.11 g, 12.80 mmol) and the resulting suspension was stirred at room temperature for 16 h. The reaction mixture was filtered through Celite and the solvent was removed in vacuo to afford 198 mg (99%) of aldehyde 9a as an orange oil. 1H NMR (CDCl3, 250.13 MHz) δ 1.03 (6H, s, C6''-2CH3), 1.4-1.6 (4H, m, 2 x CH2), 1.75 (3H, s, C2''-CH3), 1.8-2.0 (4H, m, 2 x CH2), 2.33 (3H, s, C3-CH3), 2.6-2.7 (4H, m, 2 x CH2), 5.99 (1H, d, J = 8.1 Hz, H2), 6.23 (1H, d, J = 15.3 Hz), 6.27 (1H, d, J = 15.8 Hz), 6.58 (1H, d, J = 15.8 Hz), 7.23 (1H, d, J = 15.3 Hz), 10.09 (1H, d, J = 8.1 Hz, H1); 13C NMR (CDCl3, 62.89 MHz) δ 13.1 (q), 19.1 (t), 21.4 (t), 21.8 (q), 28.9 (q, 2x), 33.1 (t), 33.3 (t), 33.9 (t), 34.2 (s), 39.5 (t), 126.3 (d), 129.1 (d), 129.2 (d), 130.5 (s), 131.4 (d), 131.5 (d), 136.6 (s), 138.1 (s), 145.3 (s), 155.2 (s), 191.1 (d); IR (CH2Cl2) ν 2955 (m, CH), 2922 (m, CH), 2849 (m, CH), 1654 (s, C=O), 1580 (s, C=O), 1433 (w), 1378 (w), 1199 (m), 1117 (s), 957 (w) cm^{-1}; UV (MeOH) λmax 286, 386 nm; MS m/z (%) 310 (M +, 100), 296 (28), 284 (30), 199 (21), 145 (31), 131 (28), 121 (24), 105 (29), 91 (36), 77 (20), 69 (16); HRMS [M+] calcd. for C22H32O, 312.2453; found, 312.2444.

(2E,4E)-3-Methyl-5-[2-[(E)-2-(2,6,6-trimethylcyclohex-1-en-1-yl)ethenyl]-1-cyclopenten-1-yl]-2,4-pentadienoic Acid 3a. **General Procedure**: To a solution of aldehyde 9a (160 mg, 0.51 mmol) and 2-methyl-2-butene (2.7 mL, 25.76 mmol) in t-BuOH (11 mL) was added, using a syringe pump, for a period of 73 min, 2.6 mL of a solution of NaClO2 (233 mg, 2.57 mmol) and NaH2PO4 (235 mg, 1.96 mmol) in H2O. The reaction mixture was stirred at room temperature for 10 h and then the pH was raised to pH~10 by addition of 3M NaOH. The t-BuOH was evaporated under vacuum and the remaining residue was diluted with water, saturated with NaCl and extracted with hexane. The aqueous layer was acidified to pH~3 with 0.5 N HCl and then extracted with ether (3x). The combined organic layers were dried over MgSO4, filtered and concentrated. The residue was purified by chromatography (silica, 70:30 hexane/ethyl acetate) to yield 134 mg (80%) of a yellow solid identified as the retinoic acid 3a (m.p.: 188-190 °C - hexanes/CH2Cl2; lit.:5a 193-194 °C. 1H NMR (CDCl3, 250.13 MHz) δ 0.95 (6H, s, C6~-2CH3), 1.4-1.8 (6H, m, 3 x -CH2-), 1.67 (3H, s, C3~-CH3), 2.0-2.1 (2H, m, 2H3~), 2.26 (3H, s, C3-CH3), 2.5-2.6 (4H, m, 2 x CH2), 5.74 (1H,
s, H2), 6.08 (1H, d, J = 16.0 Hz, H2), 6.14 (1H, d, J = 15.3 Hz, H4), 6.50 (1H, d, J = 16.0 Hz, H1'), 7.04 (1H, d, J = 15.3 Hz, H5); 13C NMR (CDCl3, 62.89 MHz) δ 13.6 (q), 19.0 (t), 21.2 (t), 21.6 (q, 2x), 23.9 (t), 33.2 (t), 33.7 (t), 34.0 (s), 39.4 (t), 118.2 (d), 126.4 (d), 127.8 (d), 130.0 (s), 130.5 (d), 131.9 (d), 136.4 (s), 138.0 (s), 143.5 (s), 153.7 (s), 169.5 (s); IR (CH2Cl2) υ 3600-3100 (broad, OH), 2924 (s, C-H), 2854 (m, C-H), 1665 (s, C=O), 1438 (s), 1198 (m), 1025 (m), 746 (m) cm⁻¹; UV (MeOH) λmax 272, 344 nm; MS m/z (%) 326 (M +, 100), 311 (20), 133 (17), 105 (16), 91 (21), 69 (16); HRMS [M+] calcd. for C22H32O2, 326.2246; found, 326.2248.

2-[(1E,3E)-5-Hydroxy-3-methylpenta-1,3-dien-1-yl]cyclohept-1-en-carbaldehyde 7c. In accordance with the general procedure described above, a solution of β-bromoaldehyde 5c (0.5 g, 2.46 mmol), AsPh3 (3 mg, 0.21 mmol) and Pd2(dba)3 (9 mg, 0.10 mmol) in NMP (10 mL) was treated with stannane 6 (1.11 g, 2.85 mmol) in NMP (5 mL) to afford, after chromatography, 401 mg (74%) of aldehyde 7c as an orange oil. 1H NMR (CDCl3, 400.13 MHz) δ 1.4-1.8 (6H, m, 2H 4 + 2H5 + 2H6), 1.86 (3H, s, C3'-CH3), 2.5-2.6 (4H, m, 2H3 + 2H7), 4.35 (2H, d, J = 6.7 Hz, 2H5'), 5.86 (1H, t, J = 6.7 Hz, H4'), 6.52 (1H, d, J = 15.6 Hz, H1'), 7.05 (1H, d, J = 15.6 Hz, H2), 10.18 (1H, s, CHO); 13C NMR (CDCl3, 100.61 MHz) δ 12.7 (q, C3'-CH3), 24.8 (t), 25.4 (t), 26.0 (t), 31.8 (t), 32.0 (t), 59.4 (t), 123.2 (d), 134.6 (d), 135.6 (s), 139.3 (d), 140.6 (s), 160.0 (s), 190.1 (d, CHO); IR (CH2Cl2) υ 3600-3100 (broad, OH), 2921 (s, C-H), 2851 (m, C-H), 1633 (w), 1438 (w), 1119 (w), 961 (w) cm⁻¹; UV (MeOH) λmax 240, 322 nm; MS m/z (%) 220 (M +, 12), 205 (13), 202 (71), 189 (25), 149 (100), 131 (16), 121 (15), 105 (44), 95 (10), 91 (56), 81 (18), 79 (40), 67 (24); HRMS [M+] calcd. for C14H20O2, 220.1463; found, 220.1466.

(2E,4E)-3-Methyl-5-[2-[(E)-2-(2,6,6-trimethylcyclohex-1-en-1-yl)ethenyl]-1-cyclohepten-1-yl]-2,4-pentadien-1-ol 8c. Following the general procedure, phosphonium salt 4 (2.02 g, 4.23 mmol) in THF (15 mL) was treated with n-BuLi (1.21 mL, 3.50 M in THF, 4.23 mmol) and aldehyde 7c (0.3 g, 1.40 mmol) to yield, after chromatography, 0.32 g (69%) of retinol 8c as an orange oil. 1H NMR (CDCl3, 400.13 MHz) δ 1.04 (6H, s, C6''-2CH3), 1.4-1.7 (10H, m, 5x CH2), 1.76 (3H, s, C2~CH3), 1.87 (3H, s, C3-CH3), 2.0-2.1 (2H, m, 2H3'), 2.4-2.5 (4H, m, 2x CH2), 4.30 (2H, d, J = 7.0 Hz, 2H1), 5.71 (1H, t, J = 7.0 Hz, H2), 6.16 (1H, d, J = 16.0 Hz), 6.31 (1H, d, J = 15.8 Hz), 6.63 (1H, d, J = 16.0 Hz), 6.88 (1H, d, J = 15.8 Hz); 13C NMR (CDCl3, 100.61 MHz) δ 12.8 (q), 19.2 (t), 21.9 (q), 26.1 (t), 26.2 (t), 28.8 (t), 29.0 (q, 2x), 29.5 (t), 31.8 (t), 33.0 (t), 34.2 (s), 39.5 (t), 59.4 (t), 126.6 (d, 2x), 128.9 (s), 129.4 (s), 130.8 (d), 131.0 (d), 137.3 (d), 137.4 (s), 138.3 (s), 140.4 (s); IR (CH2Cl2) υ 3600-3100 (broad, OH), 2921 (s, CH), 2851 (m, CH), 1633 (w), 1438 (w), 1119 (w), 961 (w) cm⁻¹; UV (MeOH) λmax 254, 320 nm; MS m/z (%) 340 (M +, 100), 325 (12), 309 (36), 253 (15),
(2E,4E)-3-Methyl-5-[(E)-2-(2,6,6-trimethylcyclohex-1-en-1-yl)ethenyl]-1-cyclohepten-1-yl]-2,4-pentadienal 9c. Following the general procedure, a solution of retinol 8c (40 mg, 0.12 mmol) in CH₂Cl₂ (4 mL) was treated with MnO₂ (270 mg, 3.06 mmol) at room temperature for 16 h to afford, after chromatography, retinal 9c (40 mg, 99%) as a pale orange oil. 1H NMR (CDCl₃, 400.13 MHz) δ 1.05 (6H, s, C₆-2CH₃), 1.4-1.8 (10H, m, 5 x CH₂), 1.77 (3H, s, C₂~CH₃), 2.0-2.1 (2H, m, 2H₃~), 2.33 (3H, s, C₃-CH₃), 2.5-2.6 (4H, m, 2 x CH₂), 6.01 (1H, d, J = 8.2 Hz, H₂), 6.28 (1H, d, J = 15.9 Hz), 6.38 (1H, d, J = 15.9 Hz), 7.41 (1H, d, J = 15.6 Hz), 10.11 (1H, d, J = 8.2 Hz, H₁); 13C NMR (CDCl₃, 100.61 MHz) δ 13.3 (q), 19.1 (t), 21.9 (q), 25.9 (t), 26.0 (t), 28.5 (t), 29.0 (q, 2x), 30.1 (t), 31.6 (t), 33.0 (t), 34.2 (s), 39.4 (t), 128.9 (d), 129.1 (d), 129.4 (d), 129.9 (s), 130.5 (d), 133.8 (d), 137.1 (s), 138.2 (s), 146.0 (s), 155.8 (s), 191.1 (d); IR (CH₂Cl₂) υ 2960 (s, CH), 2936 (s, CH), 2851 (m, CH), 1657 (s, C=O), 1580 (s, C=C), 1343 (w, C=C), 1198 (m), 1118 (m), 957 (m) cm⁻¹; UV (MeOH) λmax 226, 260, 288, 386 nm; MS m/z (%) 338 (M⁺, 100), 324 (30), 269 (26), 256 (28), 239 (18), 225 (19), 213 (23), 201 (97), 187 (22), 173 (35), 160 (65), 145 (39), 131 (40), 119 (34), 105 (56), 91 (72), 81 (50), 69 (50); HRMS [M⁺] calcd. for C₂₄H₃₆O, 338.2610; found, 338.2610.

(2E,4E)-3-Methyl-5-[(E)-2-(2,6,6-trimethylcyclohex-1-en-1-yl)ethenyl]-1-cyclohepten-1-yl]-2,4-pentadienoic Acid 3c. Following the general procedure for oxidation of aldehydes to carboxylic acids, retinal 9c (89 mg, 0.26 mmol) was treated with a solution of NaClO₂ (117 mg, 1.30 mmol) and NaH₂PO₄ (118 mg, 0.98 mmol) in H₂O (1.3 mL) in the presence of 2-methyl-2-butene (1.3 mL, 13.0 mmol) and t-BuOH (5.5 mL) to yield, after chromatography, retinoic acid 3c (75 mg, 81%) as a yellow solid (m.p.: 139-141 °C - hexanes/CH₂Cl₂; lit.:⁵a 143-145 °C). 1H NMR (CDCl₃, 400.13 MHz) δ 1.05 (6H, s, C₆-2CH₃), 1.4-1.7 (8H, m, 4 x CH₂), 1.76 (3H, s, C₃-CH₃), 1.7-1.8 (2H, m, CH₂), 2.05 (2H, t, J = 6.2 Hz, CH₂), 2.37 (3H, s, C₂~CH₃), 2.5-2.8 (4H, m, 2 x CH₂), 5.84 (1H, s, H₂), 6.25 (1H, d, J = 16.0 Hz, H₂), 6.34 (1H, d, J = 16.0 Hz, H₄), 6.63 (1H, d, J = 16.0 Hz, H₁); 13C NMR (CDCl₃, 100.61 MHz) δ 13.3 (q), 19.2 (t), 21.5 (q), 26.0 (t), 26.1 (t), 28.5 (t), 29.0 (q, 2x), 30.0 (t), 31.7 (t), 33.0 (t), 34.2 (s), 39.5 (t), 117.2 (d), 128.3 (s), 128.8 (d), 129.6 (d), 130.6 (d), 133.3 (d), 137.0 (s), 138.2 (s), 144.7 (s), 156.1 (s), 171.9 (s, CHO); IR (CH₂Cl₂) υ 3100-3600 (broad, OH), 2952 (m, CH), 2922 (s, CH), 2852 (m), 1682 (s, C=O), 1584 (s), 1446 (m), 1254 (m), 1178 (m), 1036 (m), 955 (w), 808 (m), 661 (m) cm⁻¹; UV (MeOH) λmax 270, 336 nm. MS m/z (%) 354 (M⁺, 32), 339 (6), 270 (5), 255 (10), 230 (16), 216 (10), 194
Following the general procedure described above for the preparation of hydroxy aldehyde 3a, a solution of β-bromoaldehyde 5d (1.38 g, 6.38 mmol), AsPh₃ (98 mg, 0.32 mmol), Pd₂(dba)₃ (292 mg, 0.32 mmol) and vinylstannane 6 (2.96 g, 7.65 mmol) in NMP (74 mL) was stirred at room temperature to afford, after chromatography, 1.20 g (80%) of aldehyde 7d as a dark orange oil. 

$$\delta$$ 1.4-1.5 (4H, m, 2H₅ + 2H₆), 1.5-1.6 (2H, m, 2H₄), 1.6-1.7 (2H, m, 2H₇), 1.86 (3H, s, C₃''-CH₃), 2.4-2.5 (2H, m, 2H₃), 2.6-2.7 (2H, m, 2H₈), 4.34 (2H, d, J = 6.6 Hz, 2H₅''), 5.85 (1H, t, J = 6.6 Hz, H₄'), 6.55 (1H, d, J = 15.6 Hz), 7.06 (1H, d, J = 15.6 Hz), 10.25 (1H, s, CHO); 13C NMR (CDCl₃, 100.61 MHz) δ 12.6 (q), 25.0 (t), 26.0 (t), 27.0 (t), 29.2 (t), 29.6 (t), 30.2 (t), 59.3 (t), 122.2 (d), 134.5 (d), 135.6 (s), 138.7 (s), 139.3 (d), 156.1 (s), 190.3 (s); IR (NaCl) $\nu$ 3600-3200 (broad, OH), 2925 (s, CH), 2850 (m, C-H), 1655 (s), 1597 (m, C=C), 1447 (m), 1014 (m), 955 (m) cm⁻¹; UV (EtOH) $\lambda_{max}$ 240, 322 nm; MS m/z (%) 234 (M⁺, 11), 216 (81), 203 (24), 163 (56), 159 (13), 147 (11), 131 (14), 121 (14), 117 (17), 105 (44), 91 (38), 83 (100), 79 (24), 67 (17); HRMS [M⁺] calcd. for C₁₅H₂₂O₂, 234.1621; found, 234.1620.

Following the general procedure, phosphonium salt 4 (6.34 g, 13.24 mmol) in THF (25 mL) was treated with n-BuLi (5.6 mL, 2.37 M in THF, 13.24 mmol) and then with a solution of aldehyde 7d (1.0 g, 4.27 mmol) in THF (20 mL) to yield, after chromatography, 1.10 g (73%) of retinol 8d as a yellow oil. 

$$\delta$$ 1.14 (6H, s, C₆''-2CH₃), 1.4-1.7 (12H, m, 6x CH₂), 1.62 (3H, s, C₂''-CH₃), 1.87 (3H, s, C₃''-CH₃), 1.9-2.0 (2H, m, 2.5-2.6 (2H, m), 4.00 (2H, d, J = 6.7 Hz, 2H₁), 5.63 (1H, t, J = 6.7 Hz, H₂), 6.39 (1H, d, J = 15.7 Hz), 6.47 (1H, d, J = 15.7 Hz), 6.99 (1H, d, J = 16.0 Hz), 7.11 (1H, d, J = 16.0 Hz); 13C NMR (C₆D₆, 100.61 MHz) δ 12.7 (q), 19.7 (t), 22.2 (q), 27.2 (t), 27.3 (t), 27.6 (t), 28.1 (t), 28.6 (q, 2x), 30.4 (t), 30.6 (t), 33.3 (t), 34.5 (s), 39.9 (t), 59.3 (t), 125.5 (d), 127.4 (d), 128.8 (s), 131.1 (d), 131.7 (d), 132.6 (d), 135.6 (s), 136.2 (s), 137.1 (s), 138.8 (s); IR (NaCl) $\nu$ 3600-3100 (broad, OH), 2925 (s, CH), 2853 (m, CH), 1714 (w), 1449 (m), 1216 (m), 961 (w), 757 (s) cm⁻¹; UV (EtOH) $\lambda_{max}$ 252, 292 nm; MS m/z (%) 354 (M⁺, 100), 339 (16), 323 (24), 309 (10), 283 (11), 267 (8), 253 (14), 239 (15), 227 (11), 213 (12), 199 (10), 187 (14), 169 (11), 157 (15), 143 (17), 131 (17), 119 (15), 105 (24), 91 (24), 81 (21), 69 (21); HRMS [M⁺] calcd. for C₂₅H₃₈O, 354.2923; found, 354.2921.
3.39 mmol) at room temperature for 16 h to afford, after chromatography, retinal 9d (51 mg, 85%) as a dark yellow oil. 1H NMR (CDCl₃, 400.13 MHz) δ 1.18 (6H, s, C₆–2CH₃), 1.4-1.7 (12H, m, 4 x CH₂), 1.77 (3H, s, C₂–CH₃), 1.87 (3H, s, C₃–CH₃), 2.01 (2H, t, J = 6.1 Hz, 2H), 2.47 (2H, t, J = 6.1 Hz, 2H), 2.57 (2H, t, J = 6.1 Hz, 2H), 6.06 (1H, d, J = 8.2 Hz, H₂), 6.32 (1H, d, J = 15.7 Hz, H₂'), 6.47 (1H, d, J = 16.1 Hz, H₄), 6.88 (1H, d, J = 16.1 Hz, H₁'), 7.41 (1H, d, J = 15.7 Hz, H₅), 10.05 (1H, d, J = 7.8 Hz, H₁); 13C NMR (C₆D₆, 100.62 MHz) δ 12.5 (q), 19.6 (t), 22.1 (q), 27.0 (t), 27.1 (t), 27.7 (t), 29.0 (t), 29.2 (q, 2x), 30.2 (t), 30.6 (t), 33.3 (t), 34.5 (s), 39.8 (t), 129.7 (s), 129.9 (d), 130.0 (d), 130.6 (d), 130.7 (d), 132.4 (d), 135.1 (s), 138.6 (s), 142.4 (s), 153.8 (s), 189.6 (d); IR (CH₂Cl₂) ν 2926 (s, CH), 2858 (w, CH), 1663 (m, C=O), 1590 (w, C=C), 1449 (w), 1361 (w), 1131 (w); UV (EtOH) λmax 258, 280, 338 nm; MS m/z (%): 352 (M+ +, 100), 337 (18), 323 (9), 309 (6), 283 (13), 270 (17), 253 (11), 229 (10), 215 (67), 187 (13), 174 (21), 157 (14), 145 (17), 131 (19), 119 (18), 105 (27), 91 (28), 81 (20), 69 (21); HRMS [M+] calcd. for C₂₅H₃₆O₂, 368.2768; found, 368.2767.

(2E,4E)-3-Methyl-5-[2-[(E)-2-(2,6,6-trimethylcyclohex-1-en-1-yl)ethenyl]-1-cycloocten-1-yl]-2,4-pentadienoic Acid 3d. Following the general procedure for oxidation of aldehydes to carboxylic acids, retinal 9d (50 mg, 0.14 mmol) was treated with a solution of NaClO₂ (64 mg, 0.71 mmol) and NaH₂PO₄ (65 mg, 0.54 mmol) in H₂O (0.7 mL) in the presence of 2-methyl-2-butene (0.75 mL, 7.10 mmol) and t-BuOH (2.8 mL) to yield, after chromatography, retinoic acid 3d (40 mg, 77%) as a yellow solid (m.p.: 172-174 °C-hexanes/CH₂Cl₂). 1H NMR (CDCl₃, 400.13 MHz) δ 1.05 (6H, s, C₆–2CH₃), 1.4-1.5 (6H, m, 3 x CH₂), 1.6-1.7 (6H, m, 3 x CH₂), 1.76 (3H, s, C₂–CH₃), 2.05 (2H, t, J = 6.0 Hz, 2H₁'), 2.37 (3H, s, C₃–CH₃), 2.5-2.6 (4H, m, 2 x CH₂), 5.85 (1H, s, H₂), 6.27 (1H, d, J = 16.0 Hz, H₂'), 6.35 (1H, d, J = 15.7 Hz, H₄), 6.60 (1H, d, J = 16.0 Hz, H₁'), 7.32 (1H, d, J = 15.7 Hz, H₅); 13C NMR (CDCl₃, 100.61 MHz) δ 14.4 (q), 19.6 (t), 22.3 (q), 27.1 (t), 27.2 (t), 27.9 (t), 29.1 (t), 29.4 (q, 2x), 30.3 (t), 30.6 (t), 33.4 (t), 34.7 (s), 39.9 (t), 117.6 (d), 129.9 (d), 130.0 (s), 130.3 (d), 130.6 (d), 133.0 (d), 134.8 (s), 138.7 (s), 142.4 (s), 156.4 (s), 171.7 (s); IR (NaCl) ν 2918 (s, C-H), 2847 (m, C-H), 1685 (s, C=O), 1603 (s), 1587 (s), 1542 (w), 1442 (m), 1349 (m), 1266 (s), 1186 (s), 957 (m) cm⁻¹; UV (EtOH) λmax 346 nm; MS m/z (%) 352 (M+ +, 100), 337 (18), 323 (9), 309 (6), 283 (13), 270 (17), 253 (11), 229 (10), 215 (67), 187 (13), 174 (21), 157 (14), 145 (17), 131 (19), 119 (18), 105 (27), 91 (28), 81 (20), 69 (21); HRMS [M+] calcd. for C₂₅H₃₆O₂, 368.2768; found, 368.2767.
Figure S1. Histogram of the values for the torsional angle formed by atoms C21-C10-C11-C12 in 3a-d, produced in the unbound MD simulation with all atoms unrestrained. The torsional angle refers to the one formed by the ring and the rest of the backbone of the 9-cis-retinoic acid molecule. The bin size used in this histogram is 5°, starting at an angle value of 40°.