Supporting Information:

Conformationally Defined Rexinoids and Their Efficacy in the Prevention of Mammary Cancers

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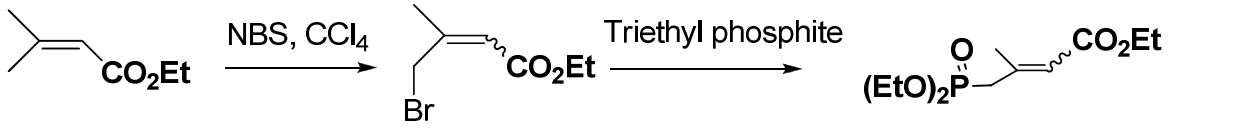
Table of Contents:

Synthesis of 4-bromo-3-methylbut-2-enoate and triethylphosphonosenecioate:



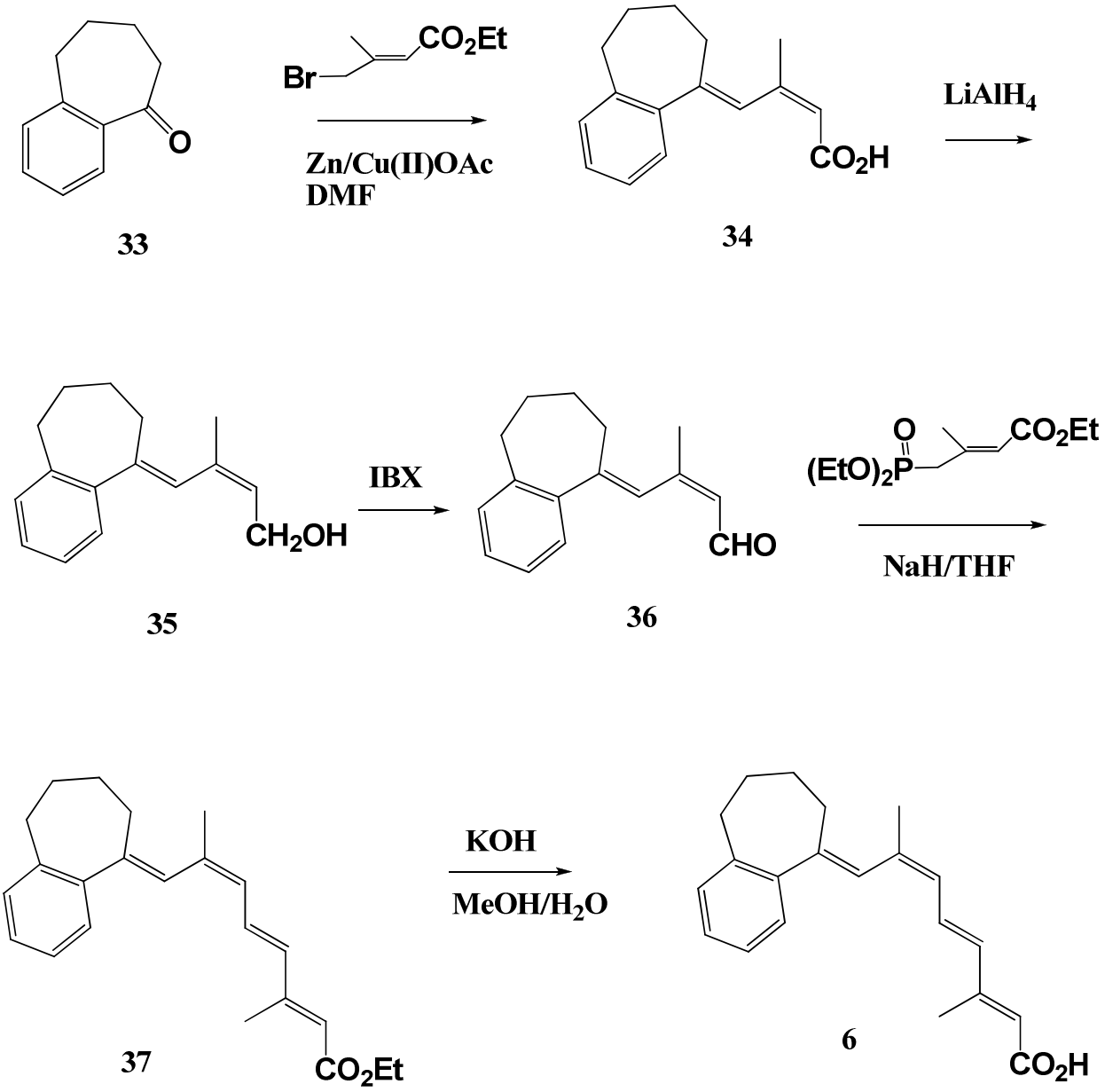
Ethyl 3,3-dimethylacrylate Ethyl 4-bromo-3-methylbut-2-enoate Triethyl phosphonosenecioate

Ethyl 4-bromo-3-methylbut-2-enoate. To a 5L, three-neck round-bottomed flask fitted with two condensers and a mechanical stirrer, was added ethyl 3,3-dimethylacrylate (100.0 g, 780 mmol) and carbon tetrachloride (1000 mL). This solution was then treated with N-bromosuccinimide (139.0 g, 781 mmol) followed by AIBN (1 g). The reaction mixture was then stirred at reflux for 6 h (CAUTION: vigorous boiling starts to take place as the reaction starts and may become uncontrollable if not cooled properly). The reaction mixture was then cooled to room temperature, filtered to remove the solids and washed with hexanes (500 mL). The organic layers were concentrated under vacuum to give an oil which was purified by distillation to give 110 g of ethyl 4-bromo-3-methylbut-2-enoate as a 1:1 mixture of *E* and *Z* isomers. B.P. 60-65^0 C (0.4 mm). ^{1}H NMR (*E* and *Z* isomers) (300 MHz, $CDCl_3$) δ5.97 (m, 1H), 5.79 (m, 1H), 4.57 (s, 2H), 4.2-4.1 (m, 4H), 3.96 (s, 2H), 2.29 (s, 3H), 2.05 (s, 3H), 1.3-1.2 (t, 6H).

Triethyl phoshonosenecioate. To a 1L, three-neck round-bottomed flask fitted with a condenser and a nitrogen inlet, was added ethyl 4-bromo-3-methylbut-2-enoate (1:1 mixture of *E* and *Z* isomers) (47.0 g, 227 mmol) and triethyl phosphite (41.5 g, 250 mmol). The reaction mixture was heated gradually to 150^0 C and maintained at this temperature for 1 h. The reaction mixture was then purified by distillation to give 51 g of triethyl phosphonosenecioate as a 1:1 mixture of *E* and *Z* isomers. bp 120-125^0 C (0.1 mm). ^{1}H NMR (*E* and *Z* isomers) (300 MHz, $CDCl_3$) δ5.7-5.8 (m, 1H), 4.1-4.2 (m, 6H), 3.5 (d, 1H), 2.7 (d, 1H), 2.3 (s, 1.5 H), 2.06 (s, 1.5 H), 1.3-1.2 (m, 9H).

Synthesis of Compound 6:

Scheme 1



(2*Z*,4*E*)-4-(6',7',8',9'-Tetrahydrobenzocyclohepten-5'-ylidene)-3-methyl-2-butenoic Acid (34).

A suspension of Zn dust (11.4 g, 175 mmol) and copper (II) acetate (1.14 g) in glacial acetic acid (50 mL) was stirred under nitrogen for 1h in a 100 mL, round-bottomed flask. The mixture was diluted with anhydrous ether (30 mL), vacuum-filtered, and the Zn-Cu complex was washed successively with anhydrous ether (3 × 25 mL) and anhydrous benzene (3 × 25 mL). This complex was dried under vacuum for 1 h and then transferred to a 250 mL, flame-dried, three-neck flask fitted with a condenser, addition funnel and nitrogen inlet. Freshly distilled dioxane (30 mL, distilled from Na/benzophenone) was

transferred to the flask and this suspension was heated to 100 °C in an oil bath. This reaction mixture was then treated dropwise with a solution of 1-benzosuberone (**33**) (8.0 g, 50 mmol) and ethyl 4-bromo-3-methylbut-2-enoate (20.7 g, 100 mmol) in dry dioxane (30 mL). Vigorous bubbling was noticed during the addition process and the reaction mixture was stirred at reflux for 8 h and then cooled to room temperature. Water (20 mL) and 2N HCl (25 mL) were added. The mixture was diluted with ether (100 mL) and allowed to stir for 10 min. The mixture was filtered and the acidic layer was separated. The organic layer was washed successively with water (75 mL), 1N NaOH (2 × 75 mL). The combined basic washes were cooled in an ice bath, acidified with 15% HCl to pH 1-2 and washed with ether (2 × 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum to give (9*Z*)-**34** as a pale yellow solid (8.4 g, 69 % yield): mp 121-122 °C (ether/*n*-hexane); UV λ_{max} 283 (ε = 7316); IR (KBr) 2978 (OH), 1666 (C=O), 1616 (C=C) cm^{-1}; MS *m/z* 243 (MH^+); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.28 (m, 1H), 7.17-7.14 (m, 2H), 7.08-7.05 (m, 1H), 6.59 (s, 1H), 5.80 (t, *J* = 1.71, 1H), 2.75 (m, 2H), 2.41-2.39 (m, 2H), 2.17 (s, 3H), 1.76-1.74 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ171.91, 156.71, 146.40, 145.01, 140.17, 128.85, 128.31, 127.96, 127.40, 126.58, 118.09, 35.55, 31.34, 29.38, 27.50, 26.03; Anal calcd. for $C_{16}H_{18}O_2$: C,79.31; H, 7.49. Found: C, 79.53; H 7.59.

(2*Z*,4*E*)-4-(6',7',8',9'-Tetrahydrobenzocyclohepten-5'-ylidene)-3-methyl-2-butenol (35). To a flame-dried two-neck round-bottomed flask fitted with a nitrogen inlet and addition funnel was added acid **34** (8.0 g, 33 mmol) and anhydrous ether (50 mL). The flask was cooled to 0 °C in an ice bath and the reaction mixture was treated with 1 M $LiAlH_4$/ether (43 mL, 43 mmol) dropwise. The reaction mixture was stirred for 2 h at 0 °C, cooled to -80 ^{0}C in a dry ice/acetone basth, and slowly quenched with methanol (2 mL) followed by 1 N HCl (15 mL). The reaction mixture was allowed to come to room temperature and extracted with ether (2 × 75 mL). The combined ether layers were washed with water (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated under vacuum to give the alcohol **35** (7.2 g, 95% yield) as a an oil: UV λ_{max} 239 (ε = 11263); IR (neat) 3326 (OH), 1710 (C=C) cm^{-1}; MS *m/z* 211 ($MH^+ - H_2O$); ^{1}H NMR (300 MHz, $CDCl_3$) δ7.19-7.14 (m, 3H), 7.11-7.07 (m, 1H), 5.92 (s, 1H), 5.56 (m, 1H), 4.20 (d, *J* = 6.9, 2H), 2.75 (m, 2H), 2.32 (m, 2H), 1.91 (s, 3H), 1.73 (m, 4H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ145.86, 145.32, 140.53, 136.52, 129.21, 128.58, 127.59, 126.75, 126.70, 60.90, 36.19, 30.92, 29.79, 27.87, 24.62; Anal. calcd for $C_{14}H_{16}O$: C, 84.16; H, 8.83. Found: C, 83.95; H, 8.87.

(2*Z*,4*E*)-4-(6',7',8',9'-Tetrahydrobenzocyclohepten-5'-ylidene)-3-methyl-2-butenal (36). A single-neck, round-bottomed flask fitted with a reflux condenser was charged with *o*-iodoxybenzoic acid (IBX) (34.4 g, 123 mmol) and acetone (75 mL) and warmed to 50-55 °C in an oil bath. A solution of alcohol **35** (7.0 g, 31 mmol) in acetone (25 mL) was added all at once to the reaction mixture. The reaction was then allowed to stir at 50-55 °C for 1.5 h. The reaction mixture was cooled to 0 ^{0}C in an ice bath, diluted with ether (100 mL) and filtered through a sintered glass funnel. The filtrate was washed with ether (2 × 50 mL), and the combined ether layers were concentrated under vacuum to furnish crude product **36** (5.8 g, 84% yield). This was purified by flash column chromatography (*n*-hexane/ether: 4/1) to give 9*Z*-aldehyde **36** (5.1 g, 74% yield): UV λ_{max} 232 (ε = 13714); IR (KBr) 1675 (C=0), 1612 (C=C) cm^{-1}; MS *m/z* 227.2 (MH^+); ^{1}H NMR (300 MHz, $CDCl_3$) δ9.92 (d, *J* = 8.3 Hz, 1H), 7.23-7.19 (m, 3H), 7.15-7.10 (m, 1H), 6.17 (s, 1H), 6.01 (d, *J* = 8.3 Hz, 1H), 2.80-2.75 (m, 2H), 2.41-2.38 (m, 2H), 2.13 (s, 3H), 1.75-1.73 (m, 4H) ^{13}C NMR (75 MHz, $CDCl_3$) δ193.34, 160.15, 148.97, 143.98, 140.22, 129.26, 129.20, 128.08, 127.97, 126.62, 125.58, 35.72, 30.94, 29.20, 27.31, 25.56; Anal. calcd for $C_{16}H_{18}O$: C, 84.92; H, 8.02. Found: C, 84.64; H, 8.20.

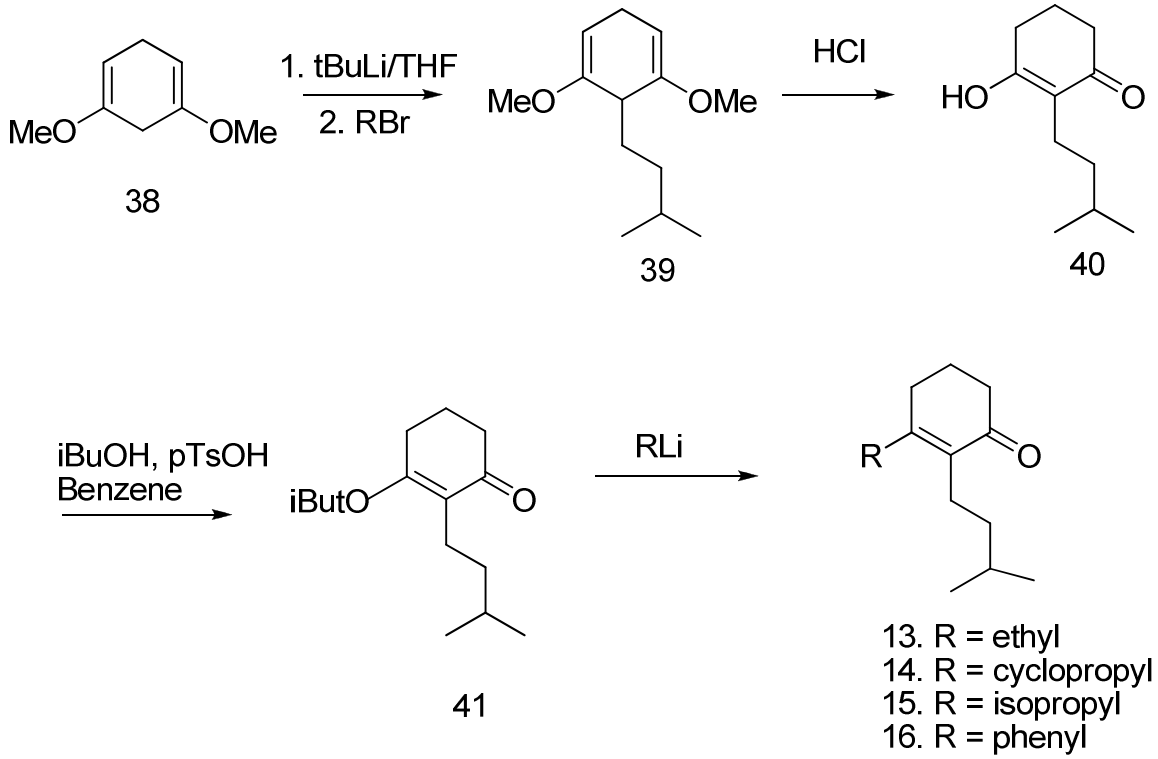
(2*E*,4*E*,6*Z*,8*E*)-Ethyl 8-(6',7',8',9'-Tetrahydrobenzocyclohepten-5'-ylidene)-3,7-dimethyl-2,4,6-octatrienoate (37). To a flame-dried, 250 mL, tree-neck round-bottomed flask fitted with a nitrogen inlet, addition funnel and rubber septum was added NaH (60% suspension in mineral oil, 0.96 g, 24

mmol). Dry THF (30 mL, distilled over Na/benzophenone) was added to the flask followed by a solution of phosphonosenecioate (6.34 g, 24 mmol) in dry THF (20 mL). The resulting solution was stirred for 15 min. and then freshly distilled HMPA (7.5 mL) was added under a nitrogen atmosphere. The flask was covered with aluminum foil and stirred for 15 more min. A solution of aldehyde **36** (5.0 g, 22 mmol) in dry THF (25 mL) was added dropwise through the addition funnel, and the mixture was then stirred for 2.5 h. The reaction mixture was quenched with water (25 mL) and extracted with ether (2 × 75 mL). The combined ether layers were washed with brine (75 mL), dried over Na_2SO_4 and concentrated under vacuum to furnish the crude product. The product was purified by column chromatography (*n*-hexane/ether: 9/1) to gave 5.9 g of **36** as a 85:15 mixture of (9*Z*) : (9*Z*,13*Z*)-**36** (80% combined yield). Separation of these isomers was achieved by column chromatography using *n*-hexane/benzene (1:1) to obtain pure (9*Z*)-**36** (4.6 g, 62% yield) as a yellow oil: UV λ_{max} 324 nm (ε = 28516); IR (neat) 1707 (C=O), 1605 (C=C) cm^{-1}; MS *m/z* 337 (MH^+); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.18 (m, 3H), 7.14-7.09 (m, 1H), 6.87 (dd, *J* = 4.3 & 11.0 Hz, 1H), 6.22 (d, *J* = 15.3 Hz, 1H), 6.09 (d, *J* = 11.07 Hz, 1H), 6.06 (s, 1H), 5.76 (s, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.80-2.75 (m, 2H), 2.38-2.34 (m, 2H), 2.28 (s, 3H), 2.02 (s, 3H), 1.73-1.71 (m, 4H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.62, 153.24, 146.40, 145.30, 140.97, 140.45, 134.21, 132.93, 129.25, 128.41, 127.99, 127.81, 126.77, 118.99, 60.06, 35.95, 31.13, 29.22, 27.70, 24.99, 14.78, 14.16; Anal. Calcd for $C_{23}H_{28}O_2$: C, 82.10; H, 8.51. Found: C, 81.86; H, 8.51.

(2*E*,4*E*,6*Z*,8*E*)-8-(6',7',8',9'-Tetrahydrobenzocyclohepten-5'-ylidene)-3,7-dimethyl-2,4,6-octatrienoic Acid (6). The 9*Z*-ester **36** (4.0 g, 12 mmol) was suspended in methanol (200 mL) and warmed to about 70 °C in an oil bath. An aqueous solution of 1.25 N KOH (150 mL, 120 mmol) (prepared with distilled and degassed water) was added to the above suspension and stirred under reflux for 1 h. Then the reaction mixture was cooled in an ice bath, diluted with ice-cold water (100 mL) and acidified to pH 1-2 with ice-cold 2 N HCl. The resulting precipitate was filtered under vacuum and redissolved in ether (100 mL), washed with brine (40 mL), dried over Na_2SO_4 and concentrated under vacuum to furnish the final acid **6** (3.5 g, 96% yield) as a yellow solid, which was crystallized from ether/*n*-hexane to furnish highly pure (9*Z*)-**6** (2.4, 67% yield): mp 174-175 °C (ether/*n*-hexane); UV λ_{max} 319 (ε = 32722); IR (KBr) 2928 (OH), 1669 (C=O), 1595 (C=C) cm^{-1}; MS *m/z* 209.5 (MH^+); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.5 (bs, 1H), 7.24-7.17 (m, 3H), 7.12-7.10 (m, 1H), 6.92 (dd, *J*= 11.00 & 4.28 Hz, 1H), 6.25 (d, *J* = 15.3 Hz, 1H), 6.11 (d, *J* = 10.91, 1H), 6.07 (s, 1H), 5.79 (s, 1H), 2.81-2.77 (m, 2H), 2.38-2.34 (m, 2H), 2.29(s, 3H), 2.03 (s, 3H), 1.73 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.63, 155.83, 146.55, 145.24, 141.81, 140.45, 133.99, 133.86, 129.27, 128.40, 127.94, 127.75, 127.71, 126.77, 35.94, 31.13, 29.21, 27.68, 25.04, 14.37; Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.65; H, 7.84.

Synthesis of Starting Ketones 13-16:

Scheme 1



2-(3-methyl) butyl-1,3-dimethoxy-1,4- butadiene (39): A solution of diene **38** (60.1 g, 429.4 mmol) in anhydrous THF (650 mL), in a 5L, three neck round bottomed flask under nitrogen atmosphere was cooled to –78 ^{0}C in dry ice/acetone bath. This solution was slowly treated with tert. BuLi (1.7 M sol. in pentane, 278 mL, 472.2 mmol). (**CAUTION**: tert. BuLi is highly pyrophoric and should be handled with proper care). The resulting golden yellow solution was allowed to stir for 15 minutes, during which a fine precipitate developed. To this was slowly added freshly distilled 1-bromo-3-methyl butane (110 g, 728.5 mmol), and the mixture was stirred at –78 C for 15 min. The cold bath was removed and the mixture was allowed to stir for 2 hours. To this was added slowly 250 mL of water. The mixture was diluted with diethyl ether (200 mL) and the organic layer was separated. The aqueous layer was extracted with ether (200 mL) and the combined organic layers were washed with brine (250 mL), dried (sod.sulfate) and concentrated to give 84 g (93%) of **39** as an oil, which was used in the next step without any further purification. MS m/z 211 (M+1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.7 (t, 2H), 3.5 (s, 6H), 2.9-2.8 (m, 1H), 2.8-2.7 (m, 2H), 1.7-1.6 (m, 2H), 1.5-1.4 (m, 1H), 1.0-0.9 (m, 2H), 0.8 (d, 6H); ^{13}C NMR ($CDCl_3$) δ 155.0, 91.8, 54.6, 41.2, 33.6, 28.5, 27.8, 24.9, 23.1

2-(3-methyl) butyl-1,3-cyclohexanedione (40): A suspension of **39** (84 g, 400.0 mmol) and 1N HCl (25 mL) was heated to 90 C while stirring vigorously. After about 15 minutes the mixture became exothermic and clear homogeneous liquid. The reaction mixture was stirred for an additional 15 minutes at this temperature and cooled to room temp. During this process the product was solidified, which was diluted with water (500 mL) and filtered. The solid was suspended in hexanes (250 mL), stirred, filtered and dried to give 68 g (93.4%) of **40**. MS m/z

183 (M+1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.5-9.0 (br, 1H), 2.5 (t, 4H), 2.3-2.2 (m, 2H), 2.0-1.9 (m, 2H), 1.6-1.5 (m, 1H), 1.2-1.1 (m, 2H), 0.9 (d, 6H); ^{13}C NMR ($CDCl_3$) δ 206.0, 188.1, 117.2, 40.1, 38.1, 33.3, 28.6, 23.0, 21.2, 20.2

2-(3-methyl) butyl-3-(3-methyl) propyloxy 2-cyclohexenone (41): A solution of **40** (68 g, 373.6 mmol), isobutanol (83g, 1120 mmol), and p-toluenesulfonic acid (1 g, 1.2 mmol) in anhydrous benzene (730 mL) was refluxed overnight with azeotropic removal of water (Dean-Stark trap). The reaction mixture was cooled to room temperature, washed with saturated sodium bicarbonate solution (3 x 250 mL), brine (2 x 250 mL) and concentrated under vacuum to give 88 g (98.9%) of **41** as thick oil which solidified upon cooling. MS m/z 239 (M+1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (d, 2H), 2.5 (t, 2H), 2.3-2.2 (m, 4H), 2.0-1.9 (m, 3H), 1.6-1.5 (m, 1H), 1.2-1.1 (m, 2H), 1.0 (d, 6H), 0.9 (d, 6H); ^{13}C NMR ($CDCl_3$) δ 198.4, 171.5, 120.1, 73.9, 38.0, 36.5, 28.8, 28.4, 25.5, 22.6, 21.1, 20.1, 19.1

Procedure for making alkyl lithium's: using this general procedure, cyclopropyl lithium and ethyl lithium were prepared.

Cyclopropyl lithium. A three neck round bottomed flask containing anhydrous ether (150 mL) was treated with lithium ribbon (10 g, 1440.9 mmol) cut into small pieces. The mixture was cooled to –10 ^{0}C (methanol/ice), treated drop wise with freshly distilled cyclopropyl bromide (60 g, 495.95 mmol) in ether (200 mL). The reaction mixture was stirred for an additional 3 hours at 0-5 ^{0}C. This mixture was directly used in the next reaction without any further purification.

Procedure for preparing substituted cyclohexenones 13-16: using this general procedure, all the ketones were prepared.

2-(3-methyl) butyl -3-ethyl-2-cyclohexenone (13). A solution of isobutyl ether **41** (88 g, 369.7 mmol) in anhydrous ether (250 mL) was cooled to 0 ^{0}C in an ice bath, treated drop wise with ethyl lithium (650 mL). The resulting mixture was stirred at 0 ^{0}C for 2 hours and at room temperature for 48 hours. The reaction mixture was slowly quenched with water (200 mL), extracted with ether (2 X 200 mL). The combined organic layer was dried (Na_2SO_4), and concentrated under vacuum to provide 75 g of crude oil, which was purified by chromatography (silica gel: Hexane/ether 4:1) to give 58 g (80.1%) of **13** as an oil: MS m/z 195 (M+1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.4-2.3 (m, 4H), 2.3-2.2 (m, 4H), 1.95-1.85 (m, 2H), 1.6-1.5 (m, 1H), 1.2-1.1 (m, 2H), 1.1 (t, 3H), 0.9 (d, 6H); ^{13}C NMR ($CDCl_3$) δ 199.2, 159.9, 135.4, 39.0, 38.1, 30.0, 28.5, 27.8, 22.9, 22.6, 22.5, 12.4

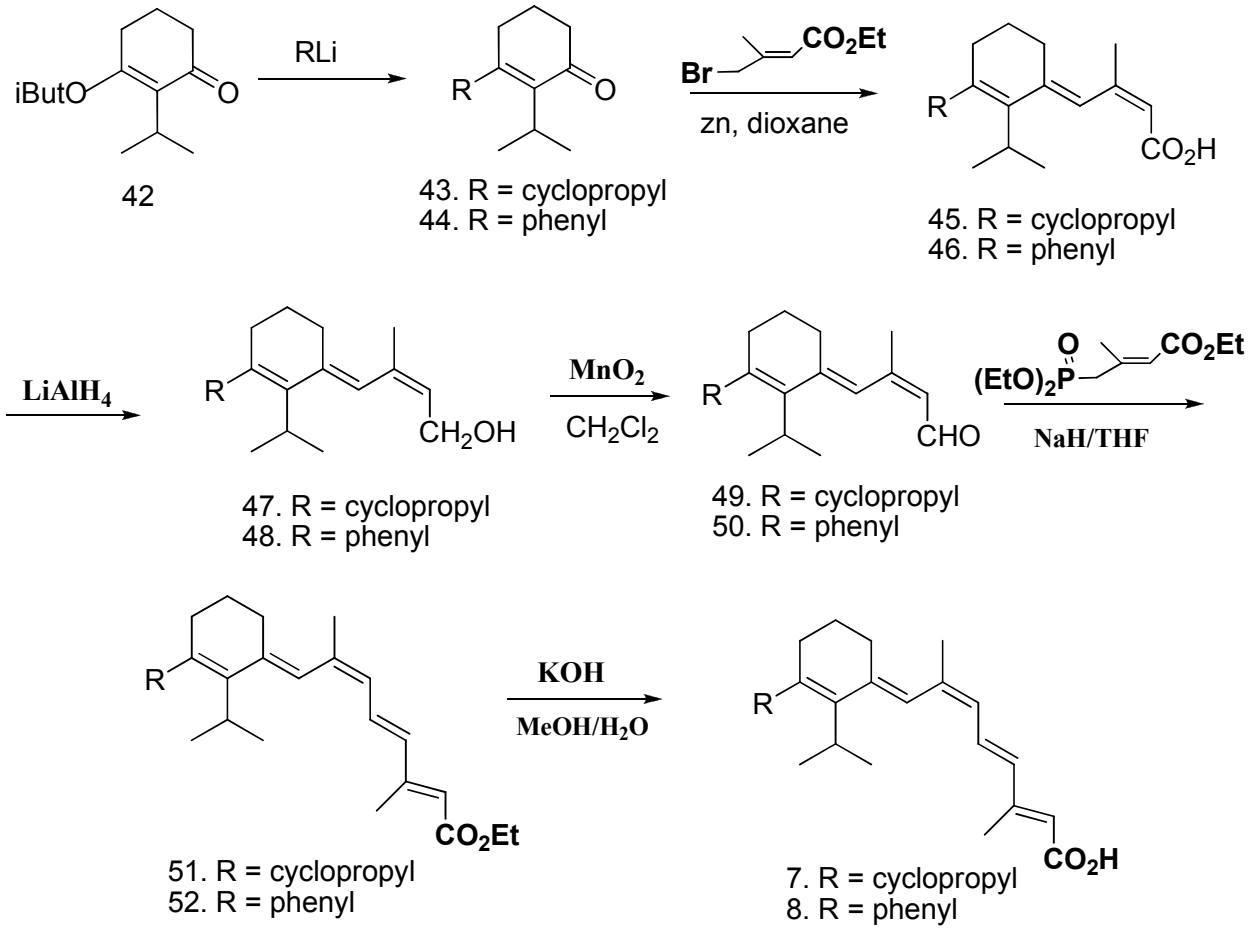
2-(3-methyl) butyl-3-cyclopropyl-2-cyclohexenone (14). MS m/z 207 (M+1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.5-2.4 (m, 2H), 2.4-2.3 (m, 2H), 1.95-1.80 (m, 5H), 1.6-1.5 (m, 1H), 1.3-1.2 (m, 2H), 0.9 (d, 6H), 0.9-0.8 (m, 2H), 0.8-0.7 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 198.3, 159.0, 136.6, 38.8, 38.3, 28.8, 24.6, 23.1, 22.9, 22.5, 14.8, 6.8

2-(3-methyl) butyl-3-isoropyl-2-cyclohexenone (15). MS m/z 209 (M+1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.0-2.9 (m, 1H), 2.38 (t, 2H), 2.3-2.2 (m, 4H), 1.9-1.8 (m, 2H), 1.6-1.5 (m, 1H), 1.2-1.1 (m, 2H), 1.06 (d, 6H), 0.90 (d, 6H); ^{13}C NMR ($CDCl_3$) δ 199.9, 163.8, 135.0, 39.5, 38.7, 31.4, 28.9, 24.9, 23.2, 23.1, 22.9, 20.7

2-(3-methyl) butyl-3-phenyl-2-cyclohexenone (16). MS m/z 243 (M+1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4-7.3 (m, 3H), 7.17 (d, 2H), 2.6 (t, 2H), 2.5 (t, 2H), 2.2-2.0 (m, 4H), 1.4-1.3 (m, 1H), 1.2-1.1 (m, 2H), 0.7 (d, 6H); ^{13}C NMR ($CDCl_3$) δ 199.9, 157.1, 141.9, 137.4, 128.7, 128.0, 127.0, 39.2, 38.6, 33.8, 28.6, 24.9, 23.2, 22.7

Synthesis of Compounds 7 and 8:

Scheme 3



42

43. R = cyclopropyl
44. R = phenyl

45. R = cyclopropyl
46. R = phenyl

47. R = cyclopropyl
48. R = phenyl

49. R = cyclopropyl
50. R = phenyl

51. R = cyclopropyl
52. R = phenyl

7. R = cyclopropyl
8. R = phenyl

2-Isopropyl-3-cyclopropyl-2-cyclohexenone (43). A solution of isobutyl ether **42** (48 g, 228.57 mmol) in anhydrous ether (150 mL) was cooled to 0 ^{0}C in an ice bath, treated drop wise with cyclopropyl lithium (350 mL). The resulting mixture was stirred at 0 ^{0}C for 2 hours and at room temperature for 8 more hours. The reaction mixture was slowly quenched with water (200 mL), extracted with ether (2 X 200 mL). The combined organic layer was dried (Na_2SO_4), and concentrated under vacuum to provide 50 g of crude oil, which was purified by chromatography (silica gel: Hexane/ether 2:1) to give the ketone **43** (38 g) as an oil: MS m/z 179 (M+1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.21-3.3 (m, 1H), 2.28-2.33 (m, 2H), 1.98-1.93 (m, 1H), 1.88-1.83 (m, 2H), 1.82-1.77 (m, 2H), 1.22 (d, 6H, J = 7.1 Hz), 0.84-0.88 (m, 2H), 0.76-0.73 (m, 2H).

2-Isopropyl-3-phenyl-2-cyclohexenone (44). MS m/z (M+1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.26 (m, 3H), 7.16-7.13 (m, 2H), 2.61-2.49 (m, 3H), 2.47-2.43 (m, 2H), 2.07-1.98 (m, 2H), 1.11 (d, 6H, J = 6.99 Hz); ^{13}C NMR ($CDCl_3$) δ 200.1, 156.89, 142.51, 140.9, 128.85, 128.12, 126.88, 39.98, 34.47, 29.95, 23.11, 21.47. Anal. (C H O) C, H.

Reformatsky reaction for preparing compounds 45 and 46:
(2Z)-4-(2'-Isopropyl-3'-cyclopropyl-2'-cyclohexen-1'-ylidene)-3-methyl-2-butenoic Acid (45). A suspension of Zn dust (133 g) in 10% HCl (400 mL) was stirred under nitrogen for 10 h in a 2 L, three-neck round bottomed flask. The aqueous layer was decanted and the zinc was

washed successively with distilled water (3 X 400 mL), anhydrous acetone (3 X 400 mL) and anhydrous ether (3 X 400 mL). After removing the residual ether the zinc dust was heated strongly with Bunsen burner flame for about a minute. The clumps of zinc are carefully broken up with a stirring rod. The cooled zinc was suspended in anhydrous dioxane (200 mL), and the stirred suspension was heated to 125 ^{0}C in an oil bath. This reaction mixture was then treated drop wise over a period of 1 h with a solution of ketone **43** (37.3 g, 212.36 mmol), and ethyl 4-bromo-3-methylbut-2-enoate (120 g, 579.43 mmol) and anhydrous dioxane (200 mL). Vigorous bubbling was noticed during the addition process and the reaction mixture was stirred at reflux for 3 hours and then cooled to temperature. Water (100 mL) and 2 N HCl (250 mL) were added. The mixture was diluted with ether (500 mL) and allowed to stir for 15 min. The mixture was filtered and the acidic layer was separated. The organic layer was washed successively with water (2 X 100 mL), 1N NaOH (3 X 150 mL). The basic wash was cooled in an ice bath, acidified with HCl (2N) to pH 1-2 and washed with ether (2 X 200 mL). The combined organic layers were washed with water (2 x 50 mL), brine (50 mL), dried (Na_2SO_4) and evaporated under vacuum to provide a semisolid. This was crystallized from hexanes/ether, filtered and dried to give pure acid **45** (30 g): mp 125-126 ^{0}C; MS m/z 261 (M+1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71 (s, 1H), 5.68 (s, 1H), 3.5-3.4 (m, 1H), 2.31-2.26 (m, 2H), 2.07 (s, 3H), 1.81-1.73 (m, 3H), 1.6-1.52 (m, 2H), 1.28 (d, 6H), 0.7-0.62 (m, 2H), 0.58-0.54 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 171.9, 157.5, 141.2, 139.8, 139.1, 121.5, 117.2, 29.5, 29.1, 27.2, 26.5, 23.1, 21.7, 15.2, 5.7. Anal. (C H O) C, H.

(2Z)-4-(2'-Isopropyl-3'-phenyl-2'-cyclohexen-1'-ylidene)-3-methyl-2-butenoic Acid (46). mp 161-163 ^{0}C; MS m/z 297 (M+1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.22 (m, 3H), 7.12-7.09 (m, 2H), 6.76 (s, 1H), 5.76 (s, 1H), 2.87-2.75 (m, 1H), 2.41-2.31 (m, 4H), 2.11 (s, 3H), 1.8-1.72 (m, 2H), 1.13 (d, 6H, J =); ^{13}C NMR ($CDCl_3$) δ 171.9, 157.3, 145.6, 140.6, 139.3, 138.6, 128.6, 127.9, 126.6, 124.6, 117.7, 35.0, 30.9, 29.6, 26.4, 23.5, 22.1. Anal. (C H O) C, H.

General procedure for preparing compounds 47 and 48:

(2Z)-4-(2'-Isopropyl-3'-cyclopropyl-2'-cyclohexen-1'-ylidene)-3-methyl-2-butenol (47). To a flame-dried three-neck round-bottomed flask fitted with a nitrogen inlet and addition funnel was added acid **45** (10 g, 38.46 mmol) and anhydrous ether (150 mL). the flask was cooled to 0 ^{0}C in an ice bath and the reaction mixture was treated with 1 M $LiAlH_4$/ether (52 mL, 51.9 mmol) dropwise. The reaction mixture was stirred for an additional 1 hour at 0 ^{0}C cooled to –78 ^{0}C in dry ice/acetone bath, and slowly quenched with methanol (50 mL) followed by 10% H_2SO_4 (100 mL). The mixture was allowed to come to room temperature extracted with ether (3 X 100 mL). The combined ether layers were washed with water (50 mL), brine (2 X 100 mL), dried (Na_2SO_4) and concentrated under vacuum to provide 10 g of colorless oil, which was used in the next reaction without further purification. MS m/z 247 (M+1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.8 (s, 1H), 5.5-5.4 (m, 1H), 4.0 (d, 2H), 2.5-2.4 (m, 2H), 2.1-2.0 (m, 2H), 1.8 (s, 3H), 1.8-1.7 (m, 3H), 1.6-1.5 (m, 3H), 1.4-1.3 (m, 2H), 1.0 (d, 6H), 0.7-0.6 (m, 2H), 0.6-0.5 (m, 2H).

(2Z)-4-(2'-Isopropyl-3'-phenyl-2'-cyclohexen-1'-ylidene)-3-methyl-2-butenol (48). MS m/z (M+1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.31 (m, 2H), 7.25-7.23 (m, 1H), 7.13-7.09 (m, 2H), 6.05 (s, 1H), 5.54-5.48 (m, 1H), 4.08 (d, 2H), 2.85-2.76 (m, 1H), 2.32 (t, 2H), 2.24-2.19 (m, 2H), 1.84 (s, 3H), 1.77-1.68 (m, 3H), 1.10 (d, 6H).

General procedure for preparing compounds 49 and 50: Using this general procedure, all the aldehydes were prepared.

(2*Z*)-4-(2'-Isopropyl-3'-cyclopropyl-2'-cyclohexen-1'-ylidene)-3-methyl-2-butenal (49). A solution of crude alcohol **47** (10 g, 40.65 mmol) in anhydrous CH_2Cl_2 (360 mL) was cooled to 0 ^{0}C in an ice bath. The reaction mixture was treated with MnO_2 (100 g), followed by powdered 4 A^0 molecular sieves (50 g) and stirred for 6 hours under nitrogen atmosphere. The reaction mixture was diluted with anhydrous CH_2Cl_2 (700 mL), stirred for 10 minutes and filtered through a 0.5 inch layer of silica gel. The MnO_2 was suspended in ether (1000 mL) stirred for 10 min and filtered. The combined organic layers were concentrated under vacuum to give 8.5 g of crude oil. This was purified by flash column chromatography (silica gel: Hexanes/ether 6:1) to give 5.1 g of 9z aldehyde **49** and 1 g of all E aldehyde. MS m/z (M+1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (d, 1H), 6.07 (s, 1H), 5.92 (dd, 1H), 3.54-3.4 (m, 1H), 2.21-2.16 (m, 2H), 2.02 (s, 3H), 1.85-1.72 (m, 3H), 1.61-1.53 (m, 2H), 1.27 (d, 6H, J =), 0.74-0.67 (m, 2H), 0.6-0.54 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 193.65, 160.96, 142.05, 139.25, 138.19, 128.41, 119.21, 28.70, 28.60, 26.90, 25.40, 23.1, 21.60, 14.73, 5.47. Anal. (C H O) C, H.

(2Z)-4-(2'-Isopropyl-3'-phenyl-2'-cyclohexen-1'-ylidene)-3-methyl-2-butenal (50). MS m/z (M+1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (d, 1H), 7.37-7.32 (m, 2H), 7.28-7.23 (m, 1H), 7.12-7.09 (m, 2H), 6.26 (s, 1H), 5.97 (d, 1H), 2.90-2.80 (m, 1H), 2.37-2.31 (m, 4H), 2.06 (s, 3H), 1.8-1.70 (m, 2H), 1.12 (d, 6H, J =); ^{13}C NMR ($CDCl_3$) δ 193.6, 160.56, 144.64, 141.40, 140.14, 137.8, 128.7, 128.3, 127.4, 126.4, 122, 34.6, 30.4, 28.8, 25.3, 23.32, 22.0. Anal. (C H O) C, H.

General procedure for preparing compounds 51 and 52:

(2*E*,4*E*,6*Z*)- and (2*Z*,4*E*,6*Z*)-Ethyl 8-(2'-Isopropyl-3'-cyclopropyl-2'-cyclohexen-1'-ylidene)-3,7-dimethyl-2,4,6-octatrienoate (51). To a flame-dried, 1L, three-neck round-bottomed flask fitted with a nitrogen inlet, addition funnel and rubber septum was added NaH (60% suspension in mineral oil, 1.2 g, 30.83 mmol). Anhydrous THF (150 mL) was added to the flask followed by a solution of freshly distilled triethylphophonosenecioate (8.1 g, 30.68 mmol) was added. The resulting solution was stirred for 15 min and then freshly distilled HMPA (25 mL) was added. The flask was covered with aluminum foil and stirred for 15 min. A solution of aldehyde **49** (5.0 g, 20.49 mmol) in dry THF (100 mL) was added dropwise through the addition funnel, and the mixture was stirred for an additional 1.5 hours. The reaction mixture was quenched with water (100 mL) and extracted with ether (3 X 250 mL). The combined ether layers were washed with brine (2 X 100 mL), dried (Na_2SO_4) and concentrated under vacuum to give 9 g of crude oil. This was purified by chromatography (silica gel: Hexanes/ether 8:1) to give 6.7 g of ester **51** as an oil (85:15 mixture of (9Z): (9Z, 13Z)-**51**). MS m/z (M+1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64 (dd, 1H), 6.18 (d, 1H), 6.01 (d, 1H), 5.96 (s, 1H), 5.72 (s, 1H), 4.15 (q, 2H), 3.53-3.43 (m, 1H), 2.25 (s, 3H), 2.15-2.06 (m, 2H), 1.90 (s, 3H), 1.85-1.73 (m, 3H), 1.59-1.50 (m, 2H), 1.30-1.20 (m, 9H), 0.70-0.65 (m, 2H), 0.58-0.55 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 167.7, 153.6, 142.44, 139.2, 138.8, 137.07, 134.05, 133.32, 126.8, 121.7, 118.3, 59.95, 29.11, 27.25, 25.14, 23.67, 22.1, 14.96, 14.76, 14.03, 5.66. Anal. (C_{24} H_{34} O_2) C, H.

(2*E*,4*E*,6*Z*)- and (2*Z*,4*E*,6*Z*)-Ethyl 8-(2'-Isopropyl-3'-phenyl-2'-cyclohexen-1'-ylidene)-3,7-dimethyl-2,4,6-octatrienoate (52). MS m/z (M+1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.3 (m, 2H), 7.28-7.2 (m, 1H), 7.16-7.13 (m, 2H), 6.69 (dd, 1H), 6.21 (d, 1H), 6.16 (s, 1H), 6.06 (d, 1H), 5.75 (s, 1H), 4.15 (q, 2H), 2.9-2.8 (m, 1H), 2.34 (t, 2H), 2.29 (s, 3H), 2.26-2.22 (m, 2H), 1.95 (s, 3H), 1.89-1.70 (m, 2H), 1.30 (t, 3H), 1.14 (d, 6H); ^{13}C NMR ($CDCl_3$) δ 167.2, 153.1, 145.1,

141.6, 139.3, 138.4, 136.9, 133.4, 133.3, 128.2, 127.6, 126.8, 126.2, 124.1, 118.2, 59.6, 34.6, 30.5, 28.8, 24.6, 23.5, 22.1, 14.4, 13.6. Anal. (C_{27} H_{34} O_2) C, H.

General procedure for preparing compounds 7 and 8:
(2*E*,4*E*,6*Z*)-8-(2'-Isopropyl-3'-cyclopropyl-2'-cyclohexen-1'-ylidene)-3,7-dimethyl-2,4,6-octatrienoic Acid (7). The ester **51**(85:15 mixture of (9Z): (9Z, 13Z)-**51**) (6.7 g, 18.93 mmol) was suspended in methanol (335 mL) and warmed to about 70 ^{0}C. An aqueous solution of KOH (2.7 *N*, 70 mL) was added to the above solution and stirred under reflux for 1 h. Then the reaction mixture was cooled in an ice bath, diluted with ice cold water (250 mL) and acidified slowly to pH 2-3 with ice cold 1N HCl. The resulting yellow precipitate was filtered and washed with ice-cold water. The wet precipitate was dissolved in ether (500 mL), washed with brine (2 X 100 mL), dried (Na_2SO_4) and concentrated to about 40 mL volume under vacuum. The mixture was diluted with hexanes (75 mL) and cooled in the freezer for 18 hours. The resulting yellow crystalline solid was filtered, washed with ice cold hexanes and dried to give 4.0 g of pure acid **7** as single 9Z isomer. mp 167-170 ^{0}C; MS m/z (M+1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 (dd, 1H), 6.21 (d, 1H), 6.02 (d, 1H), 5.96 (s, 1H), 5.74 (s, 1H), 3.53-3.43 (m, 1H), 2.25 (s, 3H), 2.1-2.04 (m, 2H), 1.90 (s, 3H), 1.85-1.73 (m, 3H), 1.6-1.50 (m, 2H), 1.29 (d, 6H), 0.70-0.62 (m, 2H), 0.58-0.53 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 172.8, 156.2, 143.3, 139.1, 139.0, 137.2, 135.0, 133.1, 126.8, 121.6, 117.4, 29.13, 29.10, 27.2, 25.2, 23.6, 22.1, 14.9, 14.3, 5.7. Anal. (C_{22} H_{30} O_2) C, H.

(2*E*,4*E*,6*Z*)-8-(2'-Isopropyl-3'-phenyl-2'-cyclohexen-1'-ylidene)-3,7-dimethyl-2,4,6-octatrienoic Acid (8). mp 202-204 ^{0}C; MS m/z (M+1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.3 (m, 2H), 7.28-7.2 (m, 1H), 7.16-7.13 (m, 2H), 6.72 (dd, 1H), 6.24 (d, 1H), 6.16 (s, 1H), 6.08 (d, 1H), 5.78 (s, 1H), 2.9-2.8 (m, 1H), 2.34 (t, 2H), 2.29 (s, 3H), 2.26-2.22 (m, 2H), 1.96 (s, 3H), 1.78-1.68 (m, 2H), 1.14 (d, 6H); ^{13}C NMR ($CDCl_3$) δ 172.8, 156.1, 145.5, 142.9, 139.8, 138.8, 137.5, 134.8, 133.4, 128.7, 128.0, 127.1, 126.6, 124.4, 117.5, 35.0, 30.9, 29.3, 25.1, 23.9, 22.5, 14.3. Anal. (C_{25} H_{30} O_2) C, H.

Table 3. Crystallographic data collection and refinement statistics for hRXRα-LBD:rexinoids **6, 9, 10** and **11** complexes with GRIP-1

Data set	**6**	**9**	**10**	**11**
PDB ID	**4RFW**	**4RMC**	**4RMD**	**4RME**
Unit Cell parameters (Å, degrees) Space group	a=b=66.39 c=111.81 α=β=γ=90 $P4_32_12$	a=b=65.85, c=112.56 α=β=γ=90 $P4_32_12$	a=b=65.97, c=112.35 α=β=γ=90 $P4_32_12$	a=b=66.17, c=112.74 α=β=γ=90 $P4_32_12$
Resolution (last shell) (Å)	50-2.4 (2.49-2.4)	50-2.7 (2.99-2.71)	50-2.4 (2.58-2.38)	50-2.3 (2.38-2.30)
No. of total/unique reflections	9557	82477/16695	127174/11698	111455/11439
R_{merge} (last shell) (%)	0.041 (0.229)	0.147 (0.186)	0.066 (0.245)	0.089 (0.219)
Redundancy (last shell)	4.8 (4.7)	4.9 (5.7)	10.9 (10.6)	9.7 (8.6)
Completeness (last shell) (%)	92.6 (86.1)	96.0 (95.9)	98.5 (96.2)	99.4 (98.4)
I/sigma (last shell)	19.3 (6.2)	14.5 (4.0)	15.7 (10.9)	24.3 (9.7)
Refinement				
no. of residues	224	224	224	224
no. of protein atoms	1788	1789	1789	1788
no. of water molecules	115	143	143	141
no. of ligand atoms	23	25	26	26
R_{cryst} (%)	21.07	19.2	20.9	21.0
R_{free} (%)	26.05	27.6	23.9	27.3
R.M.S. deviation from ideality				
bond length (Å)	0.0079	0.0040	0.0056	0.0087
bond angles (°)	1.090	1.344	1.212	1.216
Ramachandran Plot				
Most favored regions (%)	94.52	94.06	94.52	93.61
Additional allowed regions (%)	4.57	4.11	3.20	4.11

Generously allowed regions (%)	0.91	1.83	2.28	2.28
average B factor (Å^2)	46.15	35.68	25.12	41.47
non-hydrogen protein atoms (Å^2)	45.86	35.68	24.59	41.29
non-hydrogen ligand atoms (Å^2)	59.40	30.73	23.13	45.90
water molecules (Å^2)	47.26	36.72	33.12	33.43