



New retinoid chemotypes: 9-*cis*-Retinoic acid analogs with hydrophobic rings derived from terpenes as selective RAR agonists

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ABSTRACT

A series of 9-*cis*-retinoic acid analogs modified at the hydrophobic ring with a (bi)cyclohexenyl moiety derived from natural terpenes has been stereoselectively prepared using a Suzuki cross-coupling as key step. Transient transactivation studies indicate that modification of the hydrophobic ring impacts dramatically on RXR-binding and transactivation, with most retinoids being inactive on RXR β , while preserving their RAR pan-agonist profile. Furthermore, only the RAR γ subtype was capable of enantiomeric discrimination with some pairs of enantiomeric terpene-retinoids.

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1. Introduction

The pharmacological interest in retinoids, the natural and synthetic analogs of vitamin A,¹ has moved in the last two decades from the classical treatment of dermatological disorders to cancer chemoprevention.² In addition to cell proliferation, cell differentiation and apoptosis, other fundamental biological processes such as homeostasis, morphogenesis, growth, development, and immune function, are affected by retinoids. In part, these activities derive from the modulation of gene networks that starts with ligand binding to, and transactivation or repression of target genes by the retinoid subfamilies of nuclear receptors,³ namely the RXRs,⁴ which are activated by 9-*cis*-retinoic acid (**1**, Fig. 1), and the RARs,⁵ activated by both 9-*cis*-retinoic acid (**1**) and all-*trans* retinoic acid (**2**). Genetic studies in mouse confirmed earlier *in vitro* findings indicating that the functional unit transducing the retinoid signal was in fact a dimeric association of both nuclear receptors (RXR–RAR heterodimers).³ Transcription regulation of cognate gene networks upon agonist binding is initiated by a con-

formational change of the receptor (heterodimer) which triggers the dissociation of co-repressors and the association of co-activators, which in turn leads to the recruitment of chromatin modifying and transcription machineries.

Emerging details of the molecular mechanism of gene regulation have revealed a complex role for the retinoid ligand. It is undisputed that RAR agonists can autonomously activate transcription through RAR–RXR heterodimers.⁶ RXR was initially thought to be unable to bind to its own ligands (selective RXR-binding ligands are also termed rexinoids) in the context of the heterodimer unless RAR was liganded as well.⁷ However, it has become clear since that RXR can bind cognate ligands in the RAR–RXR heterodimer and that the underlying mechanism for the inability of holoRXR to activate transcription together with apoRAR is due to the fact that rexinoids are unable to dissociate co-repressors from the heterodimer (a phenomenon known as RXR subordination).⁸

In addition to RAR, other members of the nuclear receptor superfamily, such as VDR, TR, PPAR, and LXR, use RXR as heterodimerization partner, although the detailed mechanism of gene regulation by the diversity of modulators might differ. Several of those heterodimers, in particular those formed with PPARs, LXRs, or FXRs, are regarded as ‘permissive’ heterodimers to indicate that they can be activated by rexinoids alone, and structural features accounting for this permissivity have been described.⁹ The ability of RXR ligands to regulate hormonal pathways beyond the classical

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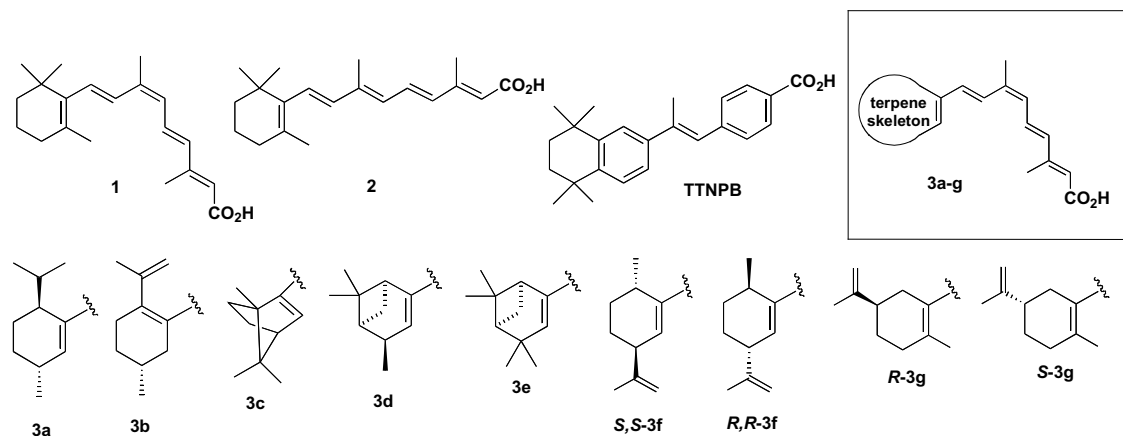


Figure 1. Retinoids and terpene-polyene chimeras from: **3a**, (–)-menthone; **3b**, (+)-pulegone; **3c**, (+)-camphor; **3d–e**, (–)-*cis*-verbanone; **3f–g**, (+) and (–)-carvone.

retinoid actions places rexinoids (agonists and antagonists) at the forefront of drug development efforts¹⁰ (see, also, for recent reviews^{11,2b}).

With a few notable exceptions,¹² most synthetic derivatives of parent retinoids **1** and **2** feature aryl rings replacing a portion of the polyene chain and/or the hydrophobic ring. These derivatives show greater stability to light, heat and acid and reduced sensitivity to enzyme degradation; synthesis is also simplified. Surprisingly, the number of alicyclic substituents of the trimethylcyclohexenyl ring of retinoids is scarce.¹³ Thus, we found of interest to develop novel analogs having hydrophobic moieties derived from alicyclic rings of natural or modified monoterpenes, with which retinoids share a common biosynthetic precursor. We want to call these novel retinoids as ‘terpene-retinoid’ chimeras since the C₁₁ polyene side chain is kept intact and only the hydrophobic region is modified with a terpenoid (Fig. 1). An advantage of the design is the fact that enantiomers of some of the starting monoterpenes are commercially available, and the hydrophobic pocket could be challenged by novel retinoids with chiral centers differing in absolute configuration. By leaving the polyene unmodified, the analysis of the biological results (gene transcriptional activities) would give an estimate of the tolerance of the protein binding pockets of RAR and RXR to modifications in the hydrophobic region of the ligand, including enantiomeric discrimination.

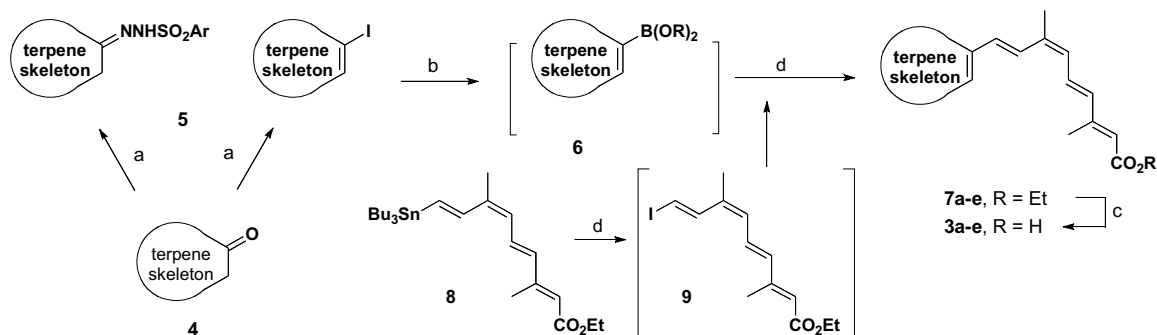
We focused primarily on the 9-*cis* stereoisomers for structural reasons: (1) Both all-*trans*-retinoic acid **2** and 9-*cis*-retinoic acid **1** act as RAR agonists; the structures of the complexes of all-*trans*-retinoic acid **2**¹⁴ and 9-*cis*-retinoic acid **1**¹⁵ bound to RAR γ are remarkable similar: 9-*cis*-retinoic acid **1** adapts to the binding pocket of RAR in a conformation resembling that of all-*trans*-retinoic acid **2** despite the marked bending of the polyene side chain

in 9-*cis*-retinoic acid **2** due to the presence of the C9–C10 *cis* double bond; (2) 9-*cis*-retinoic acid **2**, but not its all-*trans* isomer binds to and activates RXRs; (3) X-ray diffraction analysis of the ligand-binding domains of RAR γ ¹⁴ and RXR α ¹⁶ bound to 9-*cis*-retinoic acid **2** reveals that the hydrophobic ring of the ligand occupies a quite flexible region of the protein, capable of accommodating structural modifications.

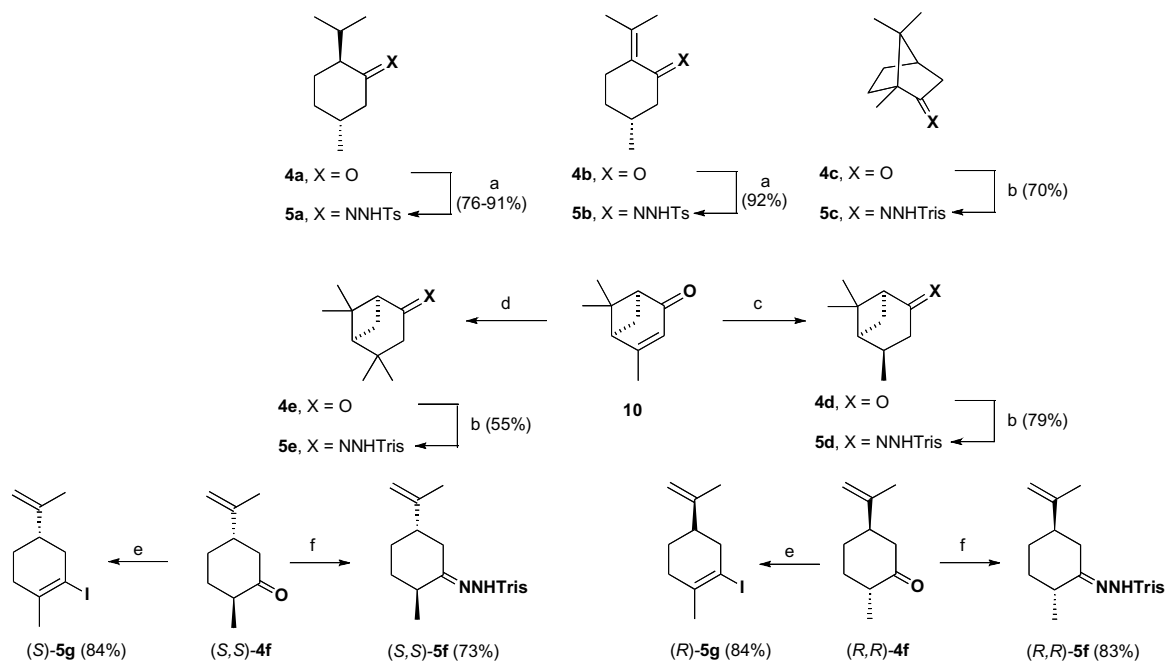
We present herein the preparation of novel 9-*cis*-retinoic acid analogs (compounds **3**, Fig. 1) that differ on the structure of the hydrophobic ring. Transient transactivation studies confirm the RAR selectivity of these analogs which, with one exception, are devoid of RXR transactivation potential.

The synthesis of these terpene-retinoid chimeras **3** having the trimethylcyclohexenyl ring in **1** replaced by other terpenoid skeletons was carried out according to our approach¹⁷ based on the C6–C7 disconnection that uses a Suzuki reaction¹⁸ to connect alkenyl fragments functionalized as iodide and boronic acid (Scheme 1). For convenience, due to the instability of the ω -iodotetraenyl ester **9**, the sequence is best carried out without isolation of the intermediates. In turn, the boronic acids were obtained by trapping with a borate the alkenyl organolithium intermediate obtained by Shapiro reaction¹⁹ of the hydrazones derived from either naturally-occurring ketones or derivatives thereof (Scheme 1). Issues of regioselectivity in the deprotonation of these hydrazones need to be solved in order to exploit the usefulness of the procedure. In one case (**5g**), the regioselective problem was solved by employing the alternative iodine–lithium exchange with a cyclohexenyliodide as precursor.

Commercially available (–)-menthone (90%) is a mixture of diastereomers (menthone and isomenthone), due to the facile epimerization of the stereocenter at C2. (–)-Menthone (**4a**) of high



Scheme 1. Reagents and conditions: (a) see Scheme 2; (b) i–RLi, solvent, –78 °C; ii–B(Oi-Pr)₃, –78 to 0 °C; iii–Pd(PPh₃)₄, iodide **9**, 10% aq TIOH 25 °C; (c) 5 N KOH, EtOH, 70 °C, 30 min; (d) I₂, CH₂Cl₂, 25 °C.



Scheme 2. Reagents and conditions: (a) TsNHNH₂, HCl, EtOH, 0 °C, 2h; (b) Tris–NHNH₂, concd HCl, CH₃CN, 25 °C. (c) Zn, NiCl₂·6H₂O, 2-methoxyethanol/H₂O, ultrasounds, 25 °C; (d) Me₂CuLi, THF; (e) i–H₂NNH₂, Et₃N, EtOH, 100 °C; ii–DBN, I₂, Et₂O, 25 °C; iii–DBN, C₆H₆, 90 °C; (f) Tris–NHNH₂, concd HCl, CH₃OH, 25 °C.

enantiomeric purity²⁰ was instead prepared from (–)-menthol by oxidation with chromic acid. Although the trisylhydrazone was the first choice for carrying out the Shapiro reaction, the slow decomposition of the derivative to 2,4,6-triisopropylbenzenesulfonic acid caused substantial epimerization at the neighboring stereogenic center. The more robust²¹ (–)-menthone tosylhydrazone (**5a**)²² was instead prepared from (–)-menthone (**4a**) after carefully monitoring the condensation reaction time.²³ (+)-Pulegone tosylhydrazone (**5b**) was obtained using the previously reported protocol.²⁴ (+)-Camphor trisylhydrazone (**5c**) was prepared accordingly using CH₃CN as solvent (Scheme 2).

(–)-*cis*-Verbanone (**4d**) was prepared in good yield (78%) from (1S)-(–)-verbenone (**10**) by reduction with ultrasound-activated Zn and NiCl₂·6H₂O in a solvent mixture of 2-methoxyethanol and water.²⁵ Treating *cis*-verbanone **4d** with trisylhydrazone in the presence of stoichiometric amounts of concd HCl produced *cis*-verbanone trisylhydrazone (**5d**). Conjugate addition of lithium dimethylcuprate to (1S)-(–)-verbenone (**10**) yielded (1S,5S)-(–)-4,4,6,6-tetramethylbicyclo[3.1.1]heptan-2-one (**4e**),²⁶ which was treated with trisylhydrazone in acetonitrile to furnish trisylhydrazone **5e** without problems (Scheme 2).²⁶

(+)- and (–)-Dihydrocarvone were obtained by reduction of the parent terpenes with Zn and NaOH in MeOH/H₂O according to the established procedure.²⁷ A modification of Barton's method, namely the oxidation of the hydrazone with I₂ in DBU and further treatment with DBU,²⁸ was selected to carry out the preparation of alkenyl iodides **5g**, with the double bond at the most substituted position of the cycloalkenyl skeleton. The kinetic deprotonation of the trisylhydrazone **5f** using the Shapiro reaction provided the less-substituted cyclohexenyl positional isomer (Scheme 2).

Following Scheme 1, hydrazones **5a–f** (or iodide **5g**) were treated with *n*-BuLi at –78 °C to generate the alkenyl anion, which was trapped with B(Oi-Pr)₃, giving the corresponding organoborane **6**. The Shapiro reactions that start from arenosulfonylhydrazones derived from (+)-pulegone tosylhydrazone (**5b**), an α,β-unsaturated ketone,²⁹ was also regioselective,³⁰ and the deprotonation of **5b** with *n*-BuLi in benzene took place at the γ position en route to **3b**.³¹ Sequential addition of Pd(PPh₃)₄, iodide **9** (generated simul-

taneously in another flask by treating tetraenylstannane **8** with a solution of I₂ in CH₂Cl₂) and a 10% aqueous solution of TIOH afforded, after 30 min reaction time (15 min for **4a** and **4d**, and 8 h for **4c**), workup and purification, pentaenyl esters **7** in high yields (63–87%). Saponification by treatment of esters **7** with 5 N KOH in MeOH at 70 °C for 30 min provided the 9-*cis*-retinoic acid analogs **3** (Scheme 1, 73–93%).

We used a cellular luciferase reporter system in order to measure the agonist and antagonist potentials of the compounds described above (compounds **3b** and **3d** were not tested) in intact cells. The HeLa-derived reporter cells were generated by introducing chimeric receptors composed of the DNA-binding domain of the yeast transcription factor GAL4 fused to the ligand-binding domain of the human RARs (RARα, β, and γ) and RXRβ. The same cells express a chimeric luciferase reporter gene constructed by fusing five repeats of the GAL4 recognition motif (17-mer) with a minimal β-globin promoter in front of the luciferase gene.

A comparison of the RAR transactivation activities reveals that all compounds display RAR pan-agonist activity at concentrations at or above 10 nM (Fig. 2). In general the novel compounds are activating at higher concentration than the potent synthetic RAR-selective pan-agonist TTNPB (Fig. 1) or 9-*cis*-RA (not shown). However, while for RARα and RARβ the maximal induction levels are below those of TTNPB and similar to those seen for 9-*cis*-RA, some of the novel retinoids (**3c**, *R*-**3g**, and *S,S*-**3f**) induce at high concentrations the RARγ-dependent transactivation to a higher level than TTNPB (Fig. 2 bottom panels). This may reflect an altered conformation induced by terpene retinoids that is more efficient in recruiting co-regulators to RARγ. We noted that *S,S*-**3f** was more potent than the *R,R* enantiomer (compare relative to TTNPB), indicating a higher affinity of the *S,S* enantiomer to RARγ and/or enantiomer-selective allosteric effects on RARγ–co-regulator interaction; no such difference was seen for RARα or RARβ.

While the parent compound 9-*cis*-retinoic acid **1** induces transcription through RAR and RXR, only one of the terpene retinoids, **3a**, displayed a significant RXR agonist activity (Fig 3A). To assess whether the new compounds could have RXR antagonist activity we exposed the reporter cells to 300 nM 9-*cis*-retinoic acid and

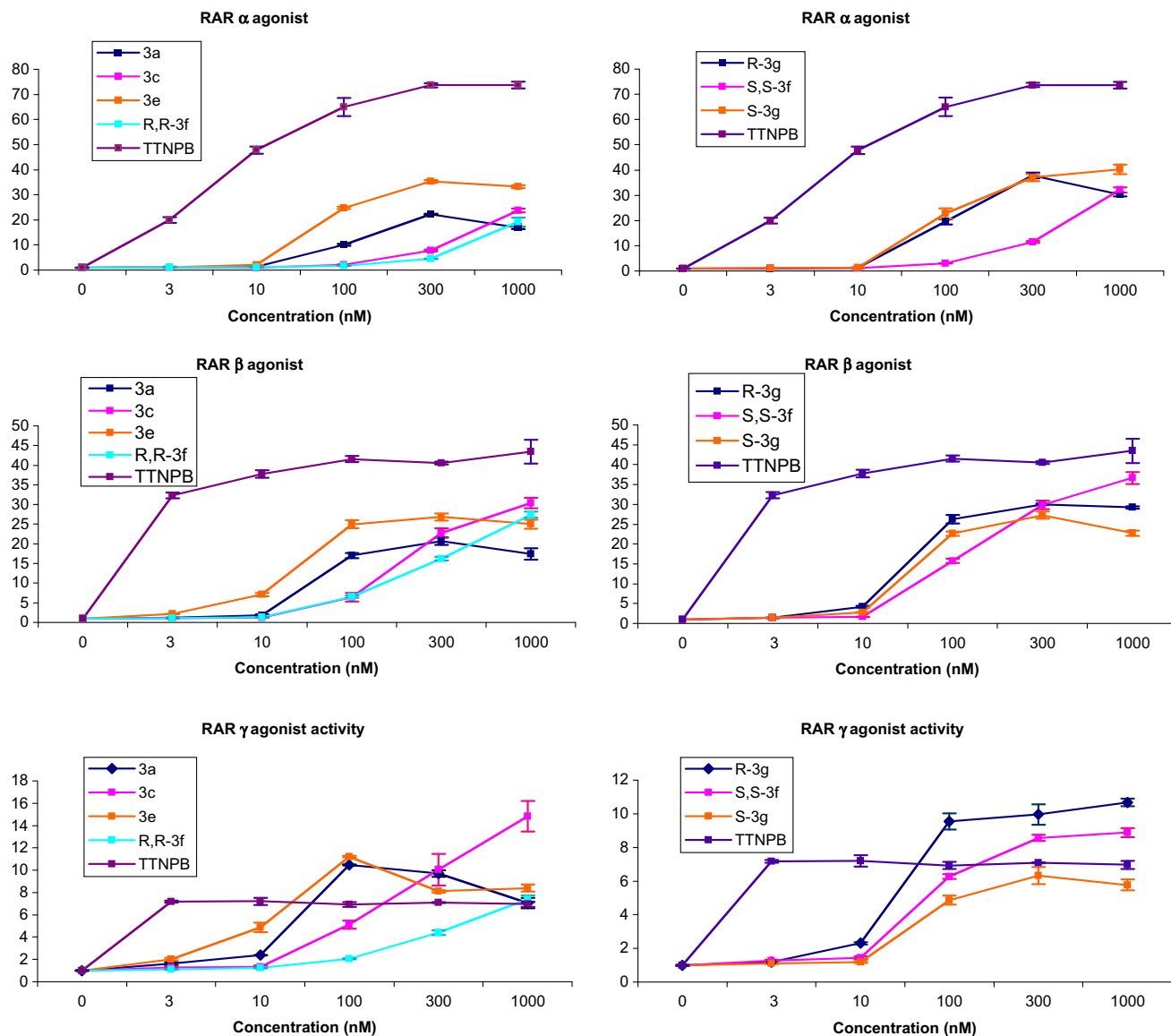


Figure 2. RAR α , β and γ selective activities of terpene retinoids. Dose response activity curves of the indicated compounds in the three RAR reporter cell lines. For comparison the activation profile of the synthetic retinoid TTNPB is shown.

increasing concentrations of the terpene-retinoid chimeras. As exemplified for **3a** and *S,S-3f* (Fig. 3B) very weak, if any, antagonist activity was observed. Taken together the data reveal that the present terpene retinoids are pan-RAR agonists with low (**3a**) or no (other terpene retinoids) RXR agonist and no RXR antagonist activities.

The lack of transactivation potential of the terpene retinoids (except for **3a**) through RXR is intriguing. Relative to RAR γ , 9-*cis*-retinoic acid in RXR α shows a higher bending angle (70° vs 60°) and a 2.7 Å shift towards the center of the cavity (Fig. 4). The ca. 90° rotation of the C8–C9 bond is imposed on the ligand by a hydrophobic pocket that lies 9 Å away from the location of the binding site for the β -ionone ring in RAR γ . The slightly lower activity of this ligand with RAR γ must be a consequence of the smaller number of hydrophobic contacts (67 for RXR α -9-*cis*-retinoic acid; 83 for RAR γ -9-*cis*-retinoic acid; at a 4.2 Å distance cut-off).

From the analysis of the orientations of the β -ionone rings in RXR α and RAR γ and the results obtained here, it is surmised that the novel 9-*cis*-retinoic acid analogs, whereas keeping the flexibil-

ity of the polyene chain that should allow them to bend towards the center of the ligand-binding cavity, however the hydrophobic ring incurs in destabilizing interactions with residues of the protein of H10-11 and H7, thus accounting for their loss of binding affinity to RXR β . Analog **3a** exceptionally must adapt to the available binding site of RXR β . Nevertheless, other structural factors, primarily the *s-cis-s-trans* conformation at the C6–C7 single bond (note that only analog **3g** keeps the vinyl methyl group at the ring) that connects the hydrophobic ring to the polyene chain, may also play a role.

To summarize, the replacement of the cyclohexenyl ring of 9-*cis*-retinoic acid by structural surrogates derived from terpenes leads to synthetic retinoids that have in general lost the RXR-binding and transactivation characteristics of the parent compound, but preserve the RAR-binding and transactivation potential. Although subtype selectivity for RAR could not be achieved, the biological results suggest partial activation of RAR α , β by these terpene-retinoids and a greater activation of the RAR γ . Moreover, the latter subtype is able to discriminate between pairs of antipodes of com-

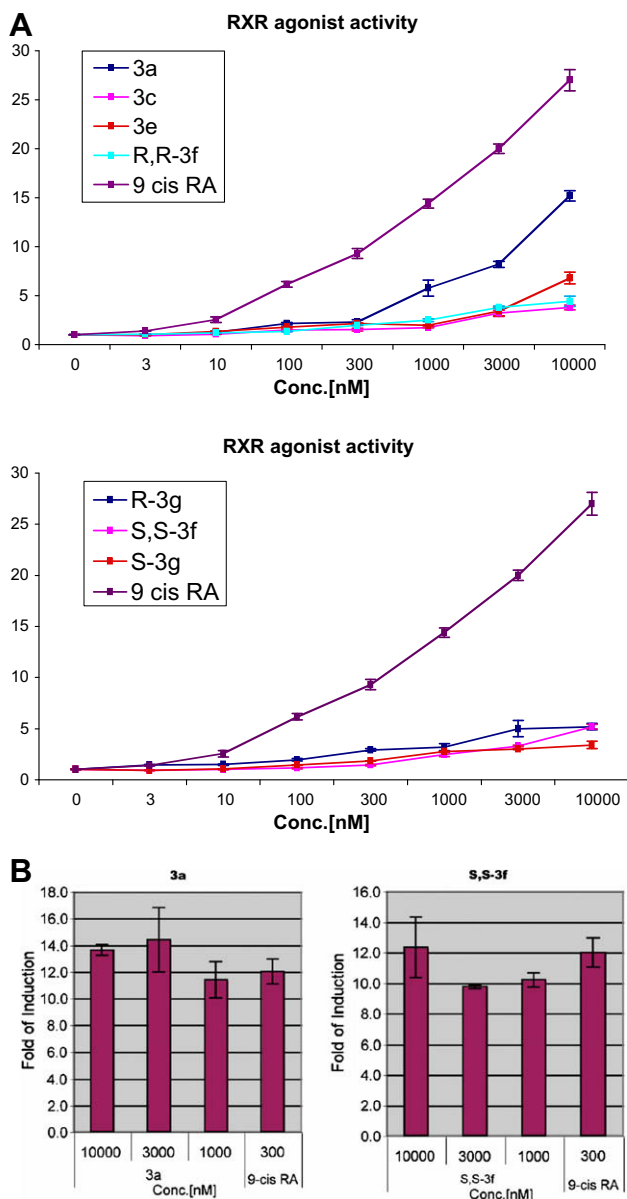


Figure 3. RXR agonist and antagonist activities of terpene retinoids. (A) Agonist dose-response activity displayed by the indicated compounds using RXR reporter cells as described in Section 2. Data are presented as fold activity over the mock-treated cells. For comparison the activity of 9-*cis*-retinoic acid (9-*cis*-RA) is shown. (B) Antagonistic potential of **3a** and S,S-**3f** in cells exposed to 300 nM 9-*cis* RA.

pound **3f**. The terpene-retinoid chimeras are useful tools to explore the available space in the hydrophobic region of the binding pocket of RAR and RXR and its effect on gene activation.

2. Experimental

2.1. General procedures

Proton (^1H NMR) and carbon (^{13}C NMR) magnetic resonance spectra were recorded in CDCl_3 , $(\text{CD}_3)_2\text{CO}$, CD_3SOCD_3 and CD_2Cl_2 . Infrared spectra (IR) were recorded in 0.1-mm path length sodium chloride cavity cells. High-resolution mass spectra (HRMS) data were recorded at an ionizing voltage of 70 eV. Analytical thin-layer chromatography was performed on Merck silica gel plates with F-254 indicator. Visualization was accomplished by UV light or a 15% ethanolic phosphomolybdic acid solution. Flash

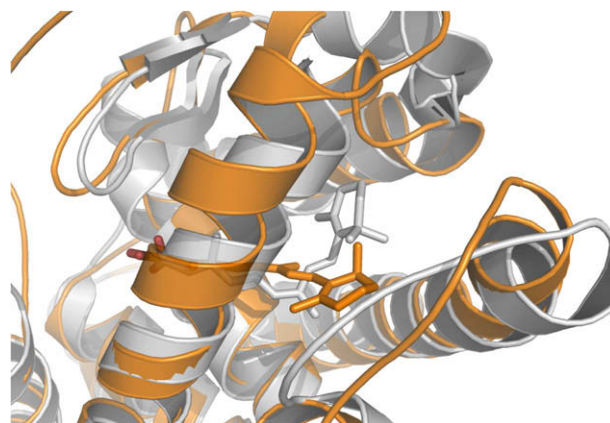


Figure 4. A comparison of the β -ionone hydrophobic pocket of 9-*cis*-retinoic acid bound to RXR α (grey) and RAR γ (orange). Looking across H3, the increase in size of the hydrophobic ring causes a clash with aminoacid residues of the neighboring helices, namely H10–11 and H7.

chromatography was performed using E. Merck silica gel 60 (230–400 mesh). All reactions were performed under a dry argon atmosphere in oven- and/or flame-dried glassware. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes or cannula. Solvents and reagents were distilled before used: tetrahydrofuran from sodium benzophenone ketyl and acetonitrile from calcium hydride. ‘Brine’ refers to a saturated aqueous solution of NaCl.

2.2. Ethyl (+)-(2*E*,4*E*,6*Z*,8*E*)-3,7-dimethyl-9-[(3*R*,6*S*)-6-isopropyl-3-methylcyclohex-1-en-1-yl]nona-2,4,6,8-tetraenoate (**3a**): general Procedure for the one-pot Shapiro–Suzuki reaction

A solution of *n*-BuLi in hexane (0.66 mL, 2.3 M, 1.54 mmol) was added to a cold ($-78\text{ }^\circ\text{C}$) suspension of **5a** (0.1 g, 0.31 mmol) in THF (1.0 mL) and the solution was stirred for 30 min. Nitrogen evolution was observed when the temperature was taken up to $0\text{ }^\circ\text{C}$, before cooling to $-78\text{ }^\circ\text{C}$ for the addition of triisopropyl borate (0.22 mL, 0.95 mmol). The mixture was stirred for 1 h at $0\text{ }^\circ\text{C}$, and then heated to room temperature. $\text{Pd}(\text{PPh}_3)_4$ (0.028 g, 0.024 mmol), followed by addition of iodide **9** [simultaneously generated by treating stannane **8** (0.12 g, 0.24 mmol) with a solution of I_2 in CH_2Cl_2] dissolved in THF (1.0 mL), were then added. After stirring for 10 min, a 10% aqueous TIOH solution was added (2.1 mL, 0.94 mmol), and the resulting mixture was stirred at $25\text{ }^\circ\text{C}$ for 30 min. It was diluted with Et_2O (2.0 mL) and filtered through Celite. The filtrate was washed with a saturated aqueous NaHCO_3 solution ($3\times$), dried (Na_2SO_4) and evaporated. The residue was purified by chromatography (SiO_2 , 95:5 hexane/ EtOAc) to afford **7a** (0.06 g, 71%) as a yellow solid. $[\alpha]_D^{24} +33.2^\circ$ (*c* 0.51, EtOH). IR (NaCl) ν 1709 (s) cm^{-1} . ^1H NMR (400.13 MHz, CDCl_3) δ 0.74 (d, $J = 6.8\text{ Hz}$, 3H), 0.98 (d, $J = 7.1\text{ Hz}$, 3H), 1.01 (d, $J = 7.1\text{ Hz}$, 3H), 1.0–1.1 (m, 1H), 1.30 (t, $J = 7.1\text{ Hz}$, 3H), 1.4–1.5 (m, 1H), 1.6–1.7 (m, 1H), 1.8–1.9 (m, 1H), 1.98 (s, 3H), 2.1–2.2 (m, 1H), 2.2–2.3 (m, 1H), 2.35 (d, $J = 1.0\text{ Hz}$, 3H), 2.4–2.5 (m, 1H), 4.17 (q, 2H, $J = 7.1\text{ Hz}$), 5.77 (s, 1H), 5.83 (s, 1H), 6.04 (d, $J = 11.5\text{ Hz}$, 1H), 6.22 (d, $J = 15.1\text{ Hz}$, 1H), 6.62 (d, $J = 15.9\text{ Hz}$, 1H), 6.80 (d, $J = 15.9\text{ Hz}$, 1H), 7.11 (dd, $J = 15.1, 11.5\text{ Hz}$, 1H) ppm. ^{13}C NMR (100.62 MHz, CDCl_3) δ 14.1, 14.8, 17.3, 21.3, 21.4, 21.7, 22.3, 29.9, 30.0, 31.2, 40.4, 60.0, 119.0, 123.2, 128.5, 130.1, 134.4, 134.8, 138.1, 138.7, 139.6, 153.1, 167.6 ppm. UV: (MeOH) λ_{max} 272, 352 nm. MS *m/z* (%) 342 (M^+ , 100), 299 (84), 269 (39), 225 (64), 183 (26), 159 (35), 157 (43), 145 (46), 131 (52), 105 (58), 91 (65). HRMS: (EI) calcd for $\text{C}_{23}\text{H}_{34}\text{O}_2$, 342.2559; found, 342.2553.

2.3. (+)-(2E,4E,6Z,8E)-3,7-Dimethyl-9-[(3R,6S)-6-isopropyl-3-methylcyclohex-1-en-1-yl]nona-2,4,6,8-tetraenoic acid (**3a**): general procedure for the hydrolysis of esters

A solution of ester (+)-**7a** (0.014 g, 0.041 mmol) in ethanol (0.1 mL) was treated with a 5 M aqueous KOH solution (0.08 mL) and then refluxed for 30 min. The solution was cooled to 25 °C, acidified with 10% HCl, and then extracted with Et₂O (3×). The combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated. The residue was purified by chromatography on silica gel (95:5 CH₂Cl₂/MeOH), to afford 0.012 g of **3a** (92%) as a yellow solid (mp 99 °C, hexane/EtOAc). [α]_D²⁴ +70.9° (c 0.1, EtOH). IR (NaCl) ν 3600–3100 (br), 1699 (s) cm⁻¹. ¹H NMR (400.13 MHz, CD₂Cl₂) δ 0.75 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 7.1 Hz, 3H), 1.1–1.9 (m, 4H), 2.01 (s, 3H), 2.1–2.3 (m, 2H), 2.35 (s, 3H), 2.4–2.5 (m, 1H), 5.82 (s, 1H), 5.88 (s, 1H), 6.09 (d, *J* = 11.5 Hz, 1H), 6.29 (d, *J* = 15.8 Hz, 1H), 6.33 (d, *J* = 15.2 Hz, 1H), 6.85 (d, *J* = 15.8 Hz, 1H), 7.21 (dd, *J* = 15.2, 11.5 Hz, 1H) ppm. ¹³C NMR (100.62 MHz, CD₃SOCD₃) δ 13.3, 17.0, 20.5, 20.8, 20.8, 21.7, 29.0, 29.1, 30.2, 39.0, 119.4, 122.8, 128.3, 129.4, 133.5, 134.5, 137.1, 137.6, 138.7, 151.6, 167.8 ppm. UV (MeOH) λ_{\max} 266, 344 nm. MS *m/z* (%) 314 (M+, 82), 271 (81), 171 (21), 149 (100), 105 (25), 91 (23), 71 (28). HRMS (EI) calcd for C₂₁H₃₀O₂, 314.2246; found, 314.2238.

2.4. Ethyl (+)-(2E,4E,6Z,8E)-3,7-Dimethyl-9-[(R)-5-methyl-2-(1-methylethen-1-yl)cyclohex-1-en-1-yl]nona-2,4,6,8-tetraenoate (**7b**)

According to the general procedure described above for the one-pot Shapiro–Suzuki reaction, tosylhydrazone **5b** (0.12 g, 0.38 mmol) in TMEDA was treated with MeLi (0.62 mL, 2.3 M in ether, 1.43 mmol), followed by B(Oi-Pr)₃ (0.17 mL, 0.75 mmol), and iodide **9** [previously generated from stannane **8** (0.15 g, 0.30 mmol)]. After stirring the mixture for 30 min at 25 °C, purification of the residue by column chromatography (SiO₂, 95:5 hexane/EtOAc) afforded **7b** (0.064 g, 63%) as a yellow solid. [α]_D²⁴ +9.9° (c 0.48, EtOH). IR (NaCl) ν 1709 (s) cm⁻¹. ¹H NMR (400.13 MHz, CDCl₃) δ 1.08 (d, *J* = 6.4 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.6–2.5 (m, 7H), 1.86 (s, 3H), 1.96 (s, 3H), 2.38 (d, *J* = 1.0 Hz, 3H), 4.18 (q, *J* = 7.1 Hz, 3H), 4.71 (dd, *J* = 2.4, 1.5 Hz, 1H), 5.03 (dd, *J* = 2.4, 0.7 Hz, 1H), 5.77 (s, 1H), 6.04 (d, *J* = 11.5 Hz, 1H), 6.22 (d, *J* = 15.0 Hz, 1H), 6.74 (d, *J* = 15.9 Hz, 1H), 6.86 (d, *J* = 15.9 Hz, 1H), 7.13 (dd, *J* = 15.0, 11.5 Hz, 1H) ppm. ¹³C NMR (100.63 MHz, CDCl₃) δ 13.9, 14.3, 21.2, 22.0, 22.5, 28.6, 30.4, 30.8, 33.7, 59.6, 114.1, 118.4, 121.2, 128.1, 128.2, 129.7, 131.8, 134.4, 138.9, 143.4, 146.3, 152.8, 167.2 ppm. UV (MeOH) λ_{\max} 230, 278 nm. MS *m/z* (%) 340 (M+, 1), 256 (5), 236 (6), 175 (6), 163 (6), 149 (7), 137 (8), 123 (9), 121 (11), 109 (10), 105 (28), 93 (16), 91 (100). HRMS (EI) calcd for C₂₃H₃₂O₂, 340.2402; found, 340.2388.

2.5. (+)-(2E,4E,6Z,8E)-3,7-Dimethyl-9-[(R)-5-methyl-2-(1-methylethen-1-yl)cyclohex-1-en-1-yl]nona-2,4,6,8-tetraenoic acid (**3b**)

According to the general procedure described above for the hydrolysis of esters, (+)-**7b** (0.040 g, 0.12 mmol) in ethanol (0.3 mL) was treated with a 5 M aqueous KOH solution (0.2 mL) and then refluxed for 30 min. Purification by chromatography (SiO₂, 95:5 CH₂Cl₂/MeOH), afforded 0.032 g of **3b** (86%) as a yellow solid (mp 155 °C, hexane/EtOAc). [α]_D²⁴ +8.9° (c 0.48, EtOH). IR (NaCl) ν 3600–3100 (br), 1715 (s) cm⁻¹. ¹H NMR (400.13 MHz, CD₂Cl₂) δ 1.13 (d, *J* = 6.4 Hz, 3H), 1.2–2.6 (m, 7H), 1.92 (s, 3H), 2.03 (s, 3H), 2.44 (d, *J* = 0.8 Hz, 3H), 4.76 (br, 1H), 5.10 (dd, *J* = 2.4, 1.5 Hz, 1H), 5.86 (s, 1H), 6.13 (d, *J* = 11.4 Hz, 1H), 6.33 (d,

J = 15.0 Hz, 1H), 6.84 (d, *J* = 15.9 Hz, 1H), 6.95 (d, *J* = 15.9 Hz, 1H), 7.28 (dd, *J* = 15.0, 11.4 Hz, 1H) ppm. ¹³C RMN (100.63 MHz, CD₂Cl₂) δ 13.8, 20.9, 21.6, 22.2, 28.6, 30.5, 30.6, 33.7, 113.7, 121.0, 128.0, 128.1, 130.7, 132.2, 134.0, 139.7, 143.6, 146.6, 146.3, 155.2, 167.5 ppm. UV (MeOH) λ_{\max} 334, 356 nm. MS *m/z* (%) 312 (M+, 63), 213 (65), 157 (55), 145 (23), 119 (25), 105 (50), 91 (36), 86 (100). HRMS (EI) calcd for C₂₁H₂₈O₂, 312.2089; found, 312.2088.

2.6. Ethyl (–)-(2E,4E,6Z,8E)-3,7-Dimethyl-9-[(1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]nona-2,4,6,8-tetraenoate (**7c**)

According to the general procedure described above for the one-pot Shapiro–Suzuki reaction, trisylhydrazone **5c** (0.164 g, 0.38 mmol) was treated with *n*-BuLi (0.39 mL, 2.9 M in hexane, 1.14 mmol), followed by B(Oi-Pr)₃ (0.18 mL, 0.75 mmol), and iodide **9** [previously generated from stannane **8** (0.15 g, 0.30 mmol)]. After stirring the mixture for 8 hours at 25 °C, purification of the residue by chromatography (SiO₂, 90:10 hexane/EtOAc) afforded **7c** (0.083 g, 81%) as a yellow solid. [α]_D²⁴ –70.7° (c 0.16, EtOH). IR (NaCl) ν 1708 (s) cm⁻¹. ¹H NMR (400.13 MHz, CDCl₃) δ 0.79 (s, 3H), 0.81 (s, 3H), 0.8–1.0 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.56 (s, 3H), 1.5–1.6 (m, 1H), 1.8–1.9 (m, 1H), 1.97 (s, 3H), 2.3–2.4 (m, 1H), 2.35 (d, *J* = 1.1 Hz, 3H), 4.17 (q, *J* = 7.1 Hz, 3H), 5.77 (s, 1H), 6.05 (d, *J* = 11.5 Hz, 1H), 6.20 (br, 1H), 6.22 (d, *J* = 15.0 Hz, 1H), 6.23 (d, *J* = 15.9 Hz, 1H), 7.08 (d, *J* = 15.9 Hz, 1H), 7.12 (dd, *J* = 15.0, 11.5 Hz, 1H) ppm. UV (EtOH) λ_{\max} 356 nm. MS *m/z* (%) 340 (M+, 57), 312 (15), 267 (14), 197 (17), 189 (11), 157 (19), 145 (12), 105 (20), 91 (100). HRMS (EI) calcd for C₂₃H₃₂O₂, 340.2402; found, 340.2397.

2.7. (–)-(2E,4E,6Z,8E)-3,7-Dimethyl-9-[(1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]nona-2,4,6,8-tetraenoic acid (**3c**)

According to the general procedure described above for the hydrolysis of esters, (–)-**7c** (0.058 g, 0.17 mmol) in ethanol (0.4 mL) was treated with a 5 M aqueous KOH solution (0.3 mL) and then refluxed for 30 min. Purification by chromatography (SiO₂, 95:5 CH₂Cl₂/MeOH), afforded 0.028 g of **3c** (53%) as a yellow solid (mp 154 °C, hexane/EtOAc). [α]_D²⁴ –80.1° (c 0.15, EtOH). IR (NaCl) ν 3400–2900 (br), 1671 (s) cm⁻¹. ¹H NMR (400.13 MHz, CD₂Cl₂) δ 0.83 (s, 6H), 0.8–2.0 (m, 5H), 1.19 (s, 3H), 2.01 (s, 3H), 2.38 (s, 3H), 5.83 (s, 1H), 6.11 (d, *J* = 11.5 Hz, 1H), 6.25 (s, 1H), 6.26 (d, *J* = 15.0 Hz), 6.30 (d, *J* = 15.5 Hz, 1H), 7.15 (d, *J* = 15.5 Hz, 1H), 7.23 (dd, *J* = 15.0, 11.5 Hz, 1H) ppm. UV (EtOH) λ_{\max} 272, 358 nm. MS *m/z* (%) 312 (M+, 35), 268 (26), 234 (25), 170 (83), 133 (32), 105 (30), 91 (40), 86 (100). HRMS (EI) calcd for C₂₁H₂₈O₂, 312.2089; found, 312.2086.

2.8. (–)-(1S,4S,5S)-4,6,6-Trimethylbicyclo[3.1.1]heptan-2-one 2,4,6-Tri-isopropylbenzenesulfonylhydrazone (**5d**)

Ketone **4d** (0.2 g, 1.31 mmol) was added with vigorous stirring to a solution of finely powdered 2,4,6-tri-isopropylbenzenesulfonylhydrazine (0.43 g, 1.45 mmol) in acetonitrile (0.5 mL) and 0.14 mL of concentrated hydrochloric acid. The reaction mixture was stirred at room temperature overnight, then cooled at 0 °C for 4 h, and the resultant white solid collected. The crude was taken up in a minimum amount of chloroform, filtered, evaporated and dried (25 °C, 0.5 mmHg) to afford 0.45 g of **5d** as a white solid (79%, mp 146 °C). [α]_D²⁴ –22.2° (c 0.045, EtOH). IR (NaCl) ν 3400–3100 (br), 1600 (m) cm⁻¹. ¹H NMR (400.13 MHz, CDCl₃) δ 0.73 (s, 3H), 1.1–1.4 (1H, m), 1.12 (d, *J* = 7.5 Hz, 3H), 1.24 (d, *J* = 6.7 Hz, 6H), 1.26 (d, *J* = 6.7 Hz, 6H), 1.27 (d, *J* = 6.7 Hz, 6H), 1.56 (s, 3H), 1.9–2.0 (m, 2H), 2.1–2.4 (m, 1H), 2.4–2.6 (m, 2H), 2.6–2.8 (m, 1H), 2.90 (sept, 1H), 4.24 (sept, 2H), 7.10 (s, 1H), 7.16 (s, 2H) ppm. ¹³C NMR (100.62 MHz, CDCl₃) δ 21.5, 23.5,

24.5, 24.8, 26.7, 29.1, 29.8, 30.5, 31.9, 34.0, 40.3, 47.2, 51.2, 123.5, 131.6, 151.3, 152.8, 163.2 ppm. MS m/z (%) 432 (M+, 11), 282 (20), 267 (13), 203 (12), 165 (100), 152 (27), 135 (10), 121 (13), 109 (11), 91 (15). HRMS (EI) calcd for C₂₅H₄₀N₂O₂S, 432.2811; found, 432.2809.

2.9. Ethyl (–)-(2E,4E,6Z,8E)-3,7-Dimethyl-9-[(1S,4S,5S)-4,6,6-trimethylbicyclo[3.1.1]hept-2-en-2-yl]nona-2,4,6,8-tetraenoate (7d)

According to the general procedure described above for the one-pot Shapiro–Suzuki reaction, hydrazone **5d** (0.13 g, 0.31 mmol) was treated with *n*-BuLi (0.40 mL, 2.3 M in hexane, 0.92 mmol), followed by B(Oi-Pr)₃ (0.14 mL, 0.61 mmol), and iodide **9** [previously generated from stannane **8** (0.12 g, 0.24 mmol)]. After stirring the mixture for 15 min at 25 °C, purification of the residue by column chromatography (SiO₂, 90:10 hexane/EtOAc) afforded **7d** (0.062 g, 75%) as a yellow solid. $[\alpha]_D^{24}$ –57.4° (c 0.04, EtOH). IR (NaCl) ν 1700 (s) cm⁻¹. ¹H NMR (400.13 MHz, CDCl₃) δ 0.92 (s, 3H), 1.12 (d, J = 7.6 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.3–1.5 (m, 1H), 1.38 (s, 3H), 1.97 (s, 3H), 2.0–2.1 (m, 1H), 2.35 (d, J = 0.9 Hz, 3H), 2.5–2.7 (m, 3H), 4.15 (q, J = 7.1 Hz, 2H), 5.69 (s, 1H), 5.75 (s, 1H), 6.03 (d, J = 11.5 Hz, 1H), 6.19 (d, J = 15.0 Hz, 1H), 6.38 (d, J = 15.7 Hz, 1H), 6.70 (d, J = 15.7 Hz, 1H), 7.08 (dd, J = 15.0, 11.5 Hz, 1H) ppm. ¹³C NMR (100.63 MHz, CDCl₃) δ 13.9, 14.4, 18.3, 21.1, 23.2, 27.3, 34.2, 37.9, 39.9, 41.5, 47.8, 59.6, 118.6, 121.3, 128.7, 129.6, 132.6, 133.0, 134.6, 138.2, 144.9, 152.7, 167.2 ppm. UV (EtOH) λ_{\max} 306, 360 nm. MS m/z (%) 340 (M+, 100), 251 (13), 213 (21), 197 (23), 171 (19), 157 (27), 145 (38), 105 (32), 91 (24). HRMS (EI) calcd for C₂₃H₃₂O₂, 340.2402; found, 340.2399.

2.10. (–)-(2E,4E,6Z,8E)-3,7-Dimethyl-9-[(1S,4R,5S)-4,6,6-trimethylbicyclo[3.1.1]hept-2-en-2-yl]nona-2,4,6,8-tetraenoic acid (3d)

According to the general procedure described above for the hydrolysis of esters, (–)-**7d** (0.047 g, 0.14 mmol) in ethanol (0.3 mL) was treated with a 5 M aqueous KOH solution (0.3 mL) and then refluxed for 30 min. Purification by chromatography (SiO₂, 95:5 CH₂Cl₂/MeOH), afforded 0.040 g of **3d** (93%), as a yellow solid (mp 117 °C, hexane/EtOAc). $[\alpha]_D^{24}$ –21.4° (c 0.49, EtOH). IR (NaCl) ν 3400–2900 (br), 1699 (s) cm⁻¹. ¹H NMR (400.13 MHz, CD₂Cl₂) δ 0.92 (s, 3H), 1.13 (d, J = 7.5 Hz, 3H), 1.2–1.4 (m, 1H), 1.39 (s, 3H), 1.99 (s, 3H), 2.0–2.2 (m, 1H), 2.35 (d, J = 0.9 Hz, 3H), 2.5–2.8 (m, 3H), 5.73 (s, 1H), 5.79 (s, 1H), 6.08 (d, J = 11.5 Hz, 1H), 6.26 (d, J = 15.0 Hz, 1H), 6.44 (d, J = 15.7 Hz, 1H), 6.76 (d, J = 15.7 Hz, 1H), 7.18 (dd, J = 15.0, 11.5 Hz, 1H) ppm. ¹³C NMR (100.63 MHz, CD₂Cl₂) δ 14.2, 18.4, 21.3, 23.5, 27.3, 34.5, 38.1, 40.4, 41.8, 48.2, 117.4, 121.6, 128.9, 130.9, 133.3, 133.7, 134.6, 139.5, 145.3, 155.8, 171.1 ppm. UV (EtOH) λ_{\max} 310 nm. MS m/z (%) 312 (M+, 18), 181 (8), 157 (10), 145 (15), 131 (9), 119 (12), 105 (30), 91 (100). HRMS (EI) calcd for C₂₁H₂₈O₂, 312.2089; found, 312.2095.

2.11. Ethyl (–)-(2E,4E,6Z,8E)-3,7-Dimethyl-9-[(1S,5S)-4,4,6,6-tetramethylbicyclo[3.1.1]hept-2-en-2-yl]nona-2,4,6,8-tetraenoate (7e)

According to the general procedure described above for the one-pot Shapiro–Suzuki reaction, hydrazone **5e** (0.17 g, 0.38 mmol) was treated with *n*-BuLi (0.62 mL, 2.3 M in hexane, 1.43 mmol), followed by B(Oi-Pr)₃ (0.17 mL, 0.75 mmol), and iodide **9** [previously generated from stannane **8** (0.15 g, 0.30 mmol)]. After stirring the mixture for 30 min at 25 °C, purification of the residue by column chromatography (SiO₂, 90:10 hexane/EtOAc) afforded **7e** (0.08 g, 79%) as a yellow solid. $[\alpha]_D^{24}$

–30.1° (c 0.54, EtOH). IR (NaCl) ν 1710 (s) cm⁻¹. ¹H NMR (400.13 MHz, CDCl₃) δ 0.97 (s, 3H), 1.03 (s, 3H), 1.12 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.3–1.5 (m, 1H), 1.43 (s, 3H), 1.8–1.9 (m, 1H), 1.99 (s, 3H), 2.38 (s, 3H), 2.4–2.5 (m, 1H), 2.5–2.7 (m, 1H), 4.17 (q, J = 7.1 Hz, 2H), 5.54 (s, 1H), 5.77 (s, 1H), 6.05 (d, J = 11.5 Hz, 1H), 6.22 (d, J = 15.0 Hz, 1H), 6.38 (d, J = 15.7 Hz, 1H), 6.72 (d, J = 15.7 Hz, 1H), 7.10 (dd, J = 15.0, 11.5 Hz, 1H) ppm. ¹³C NMR (100.63 MHz, CDCl₃) δ 13.9, 14.3, 21.1, 24.5, 26.0, 27.7, 30.0, 31.0, 39.2, 41.6, 42.0, 53.4, 59.6, 118.6, 121.5, 128.7, 129.5, 132.8, 134.6, 136.9, 138.2, 143.9, 152.7, 167.2 ppm. UV (EtOH) λ_{\max} 272, 366 nm. MS m/z (%) 354 (M+, 8), 219 (15), 191 (23), 175 (51), 149 (29), 135 (27), 119 (34), 109 (36), 107 (47), 97 (91), 91 (51), 83 (60), 69 (100). HRMS (EI) calcd for C₂₄H₃₄O₂, 354.2559; found, 354.2573.

2.12. (–)-(2E,4E,6Z,8E)-3,7-Dimethyl-9-[(1S,5S)-4,4,6,6-tetramethylbicyclo[3.1.1]hept-2-en-2-yl]nona-2,4,6,8-tetraenoic acid (3e)

According to the general procedure described above for the hydrolysis of esters, (–)-**7e** (0.03 g, 0.08 mmol) in ethanol (0.2 mL) was treated with a 5 M aqueous KOH solution (0.2 mL) and then refluxed for 30 min. Purification by chromatography (SiO₂, 95:5 CH₂Cl₂/MeOH) afforded 0.023 g of **3e** (86%), as a yellow solid (mp 187 °C, hexane/EtOAc). $[\alpha]_D^{24}$ –33.7° (c 0.08, EtOH). IR (NaCl) ν 3400–2900 (br), 1683 (s) cm⁻¹. ¹H NMR (400.13 MHz, CD₂Cl₂) δ 0.95 (s, 3H), 1.02 (s, 3H), 1.12 (s, 3H), 1.2–1.4 (m, 1H), 1.41 (s, 3H), 1.8–1.9 (m, 1H), 1.99 (s, 3H), 2.36 (s, 3H), 2.4–2.5 (m, 1H), 2.5–2.7 (m, 1H), 5.55 (s, 1H), 5.79 (s, 1H), 6.07 (d, J = 11.5 Hz, 1H), 6.26 (d, J = 15.0 Hz, 1H), 6.41 (d, J = 15.7 Hz, 1H), 6.76 (d, J = 15.7 Hz, 1H), 7.17 (dd, J = 15.0, 11.5 Hz, 1H) ppm. ¹³C NMR (100.61 MHz, CD₂Cl₂) δ 14.3, 21.3, 24.6, 26.1, 27.8, 30.1, 31.3, 39.5, 41.9, 42.5, 53.8, 117.8, 121.9, 128.9, 130.9, 133.5, 134.7, 137.5, 139.5, 144.5, 155.6, 171.9 ppm. UV (EtOH) λ_{\max} 266, 348 nm. MS m/z (%) 326 (M+, 100), 257 (27), 159 (39), 157 (30), 133 (22), 119 (35), 105 (35), 91 (40), 81 (27). HRMS calcd for C₂₂H₃₀O₂, 326.2246; found, 326.2246. Elem. Anal. Calcd for C₂₂H₃₀O₂, C, 80.94%; H, 9.26, found, C, 80.61%; H, 9.73.

2.13. (–)-(2S,5S)-2-Methyl-5-propen-2-yl-cyclohexanone 2,4,6-Tri-isopropylbenzenesulfonylhydrazone (S,S)-5f

Ketone (S,S)-**4f** (0.96 g, 6.35 mmol) was added with vigorous stirring to a solution of finely powdered 2,4,6-triisopropylbenzenesulfonylhydrazine (1.89 g, 6.35 mmol) in MeOH (7 mL) and 0.07 mL of concentrated hydrochloric acid. The reaction mixture was stirred at room temperature for 10 min, then cooled at 0 °C overnight, and the resultant white solid collected. The crude was taken up in a minimum amount of chloroform, filtered, evaporated and dried (25 °C, 0.5 mmHg) to afford 1.98 g of (S,S)-**5f** as a white solid (73%, mp 126 °C). $[\alpha]_D^{24}$ –18.31° (c 0.013, MeOH). IR (NaCl) ν 3213 (s), 3000–2800 (s), 1321, 1162 (s) cm⁻¹. ¹H NMR (400.13 MHz, CDCl₃) δ 0.96 (d, J = 6.4 Hz, 3H), 1.3–1.2 (m, 15H), 1.43 (dd, J = 12.5, 3.9 Hz, 1H), 1.7–1.6 (m, 2H), 1.74 (s, 3H), 1.82 (d, J = 13.2 Hz, 1H), 1.93 (dd, J = 13.1, 3.9 Hz, 1H), 2.03 (t, J = 12.5 Hz, 1H), 2.2–2.1 (m, 1H), 2.67 (d, J = 13.6 Hz, 1H), 2.92 (sept, J = 6.9 Hz, 1H), 4.22 (sept, J = 6.7 Hz, 2H), 4.73 (s, 1H), 4.78 (s, 1H), 7.18 (s, 2H) ppm. ¹³C NMR (100.61 MHz, CDCl₃) δ 160.9, 152.9, 151.1, 147.8, 131.3, 123.9, 123.4, 109.7, 45.2, 39.1, 35.2, 34.0, 31.3, 30.8, 29.8, 24.8, 24.7, 23.4, 20.3, 16.2 ppm. MS m/z (%) 432 (M+, 8), 282 (38), 269 (28), 189 (21), 166 (36), 165 (40), 152 (30), 121 (31), 107 (49), 93 (100), 91 (43), 81 (40), 79 (32). HRMS calcd for C₂₅H₄₀N₂O₂S, 432.2811; found, 432.2795.

2.14. (+)-(2R,5R)-2-methyl-5-propen-2-yl-cyclohexanone 2,4,6-Tri-isopropylbenzenesulfonylhydrazone (R,R-5f)

Ketone (R,R)-**4f** (0.79 g, 5.22 mmol) was added with vigorous stirring to a solution of finely powdered 2,4,6-triisopropylbenzenesulfonylhydrazine (1.56 g, 5.22 mmol) in MeOH (6 mL) and 0.054 mL of concentrated hydrochloric acid. The reaction mixture was stirred at room temperature for 10 min, then cooled at 0 °C overnight, and the resultant white solid collected. The crude was taken up in a minimum amount of chloroform, filtered, evaporated and dried (25 °C, 0.5 mmHg) to afford 1.85 g (83%) of (R,R)-**5f** as a white solid (mp 128–130 °C). $[\alpha]_D^{24} +60.5^\circ$ (c 0.11, MeOH).

2.15. Ethyl (-)-(2E,4E,6Z,8E)-3,7-Dimethyl-9-[(3S,6S)-6-methyl-3-(prop-1-en-2-yl)-cyclohex-1-ene]nona-2,4,6,8-tetraenoate (S)-7f

According to the general procedure described above for the one-pot Shapiro–Suzuki reaction, hydrazone (S)-**5f** (0.15 g, 0.35 mmol) was treated with *n*-BuLi (0.74 mL, 1.42 M in hexane, 1.06 mmol), followed by B(Oi-Pr)₃ (0.16 mL, 0.68 mmol), and iodide **9** [previously generated from stannane **8** (0.09 g, 0.17 mmol)]. After stirring the mixture for 30 min at 25 °C, purification of the residue by column chromatography (SiO₂, 95:5 hexane/EtOAc) afforded (S)-**7f** (0.044 g, 74%) as a yellow oil. $[\alpha]_D^{24} -287.2^\circ$ (c 0.31, MeOH). IR (NaCl) ν 1707 (s) cm⁻¹. ¹H NMR (400.13 MHz, (CD₃)₂CO) δ 7.30 (dd, *J* = 15.0, 11.5 Hz, 1H), 7.00 (d, *J* = 15.9 Hz, 1H), 6.39 (d, *J* = 15.9 Hz, 1H), 6.36 (d, *J* = 15.0 Hz, 1H), 6.15 (d, *J* = 11.5 Hz, 1H), 5.81 (s, 1H), 5.77 (s, 1H), 4.82 (d, *J* = 1.2 Hz, 1H), 4.61 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.9–2.7 (m, 2H), 2.35 (d, *J* = 1.2 Hz, 3H), 2.01 (s, 3H), 1.9–1.8 (m, 1H), 1.78 (s, 3H), 1.6–1.4 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.3–1.2 (m, 1H), 1.15 (d, *J* = 6.9 Hz, 3H) ppm. ¹³C NMR (100.61 MHz, (CD₃)₂CO) δ 166.2, 152.4, 148.0, 141.7, 137.9, 134.5, 133.4, 132.3, 129.7, 128.7, 122.5, 118.4, 110.9, 58.9, 42.1, 27.9, 26.5, 21.9, 21.0, 20.0, 19.3, 13.6, 12.8 ppm. UV (MeOH) λ_{\max} 268, 358 nm. MS *m/z* (%) 340 (M⁺, 36), 278 (43), 277 (100), 157 (21), 131 (26), 119 (27), 105 (36), 91 (41), 77 (48). HRMS calcd for C₂₃H₃₂O₂, 340.2402; found, 340.2402.

2.16. Ethyl (+)-(2E,4E,6Z,8E)-3,7-dimethyl-9-[(3R,6R)-6-methyl-3-(prop-1-en-2-yl)-cyclohex-1-ene]nona-2,4,6,8-tetraenoate (R)-7f

According to the general procedure described above for the one-pot Shapiro–Suzuki reaction, hydrazone (R)-**5f** (0.15 g, 0.35 mmol) was treated with *n*-BuLi (0.74 mL, 1.42 M in hexane, 1.06 mmol), followed by B(Oi-Pr)₃ (0.16 mL, 0.68 mmol), and iodide **9** [previously generated from stannane **8** (0.09 g, 0.17 mmol)]. After stirring the mixture for 30 min at 25 °C, purification of the residue by column chromatography (SiO₂, 95:5 hexane/EtOAc) afforded (R)-**7f** (0.04 g, 68%) as a yellow oil. $[\alpha]_D^{24} +75.8^\circ$ (c 0.03, MeOH). MS *m/z* (%) 340 (M⁺, 95), 278 (30), 277 (65), 253 (100), 213 (34), 157 (51), 145 (49), 133 (45), 131 (61), 119 (57), 105 (72), 91 (73), 77 (34). HRMS calcd for C₂₃H₃₂O₂, 340.2402; found, 340.2398.

2.17. (-)-(2E,4E,6Z,8E)-3,7-Dimethyl-9-[(3S,6S)-6-methyl-3-(prop-1-en-2-yl)-cyclohex-1-ene]nona-2,4,6,8-tetraenoic Acid (S)-3f

According to the general procedure described above for the hydrolysis of esters, (3S,6S)-**7f** (0.03 g, 0.1 mmol) in ethanol (0.3 mL) was treated with a 5 M aqueous KOH solution (0.2 mL) and then refluxed for 30 min. Purification by chromatography (SiO₂, 95:5 CH₂Cl₂/MeOH), afforded 0.03 g of (3S,6S)-**3f** (73%) as a yellow solid. $[\alpha]_D^{24} -126.5^\circ$ (c 0.04, MeOH). IR (NaCl) ν 3200–2700 (br), 1674 (s) cm⁻¹. ¹H NMR (400.13 MHz, (CD₃)₂CO) δ 12.8

(s, 1H), 7.29 (dd, *J* = 14.9, 11.6 Hz, 1H), 7.02 (d, *J* = 14.9 Hz, 1H), 6.5–6.3 (m, 2H), 6.17 (d, *J* = 11.5 Hz, 1H), 5.85 (s, 1H), 5.77 (d, *J* = 4.1 Hz, 1H), 4.82 (s, 1H), 4.62 (s, 1H), 2.9–2.4 (m, 3H), 2.06 (s, 3H), 2.05 (d, *J* = 2.1 Hz, 1H), 2.01 (s, 3H), 1.96 (d, *J* = 6.2 Hz, 1H), 1.81 (d, *J* = 2.7 Hz, 1H), 1.78 (s, 3H), 1.15 (d, *J* = 7.0 Hz, 3H) ppm. ¹³C NMR (100.61 MHz, (CD₃)₂CO) δ 166.9, 152.6, 148.1, 141.7, 137.8, 134.7, 133.3, 132.3, 129.6, 128.7, 122.5, 118.4, 110.8, 42.1, 27.9, 26.5, 21.9, 20.0, 19.9, 19.3, 12.7 ppm. UV (EtOH) λ_{\max} 266, 347 nm. MS *m/z* (%) 313 (25), 312 (100), 297 (19), 213 (44), 185 (32), 177 (40), 171 (28), 169 (27), 157 (63), 135 (49), 131 (59), 105 (89), 91 (95). HRMS calcd for C₂₁H₂₈O₂, 312.2089; found, 312.2089.

2.18. (+)-(2E,4E,6Z,8E)-3,7-Dimethyl-9-[(3R,6R)-6-methyl-3-(prop-1-en-2-yl)-cyclohex-1-ene]nona-2,4,6,8-tetraenoic Acid (R)-3f

According to the general procedure described above for the hydrolysis of esters, (3R,6R)-**7f** (0.022 g, 0.06 mmol) in ethanol (0.2 mL) was treated with a 5 M aqueous KOH solution (0.1 mL) and then refluxed for 30 min. Purification by chromatography (SiO₂, 95:5 CH₂Cl₂/MeOH), afforded 0.015 g of (3R,6R)-**3f** (75%) as a yellow solid. $[\alpha]_D^{24} +124.5^\circ$ (c 0.09, MeOH). MS *m/z* (%) 313 (8), 312 (32), 167 (34), 149 (100), 133 (36), 105 (35), 91 (40). HRMS calcd for C₂₁H₂₈O₂, 312.2089; found, 312.2080.

2.19. (-)-(4S)-2-Iodo-1-methyl-4-(prop-1-en-2-yl)-cyclohex-1-ene S-5g: general procedure for the Barton reaction

To a solution of (S,S)-**4f** (0.30 g, 1.97 mmol) in ethanol (6 mL) at 25 °C, was added H₂NNH₂·H₂O (1.5 mL, 49.3 mmol) and Et₃N (0.55 mL, 3.94 mmol) and the solution was stirred for 24 h at 100 °C. After cooling, the solvent was evaporated and the residue was dissolved in Et₂O and washed with a saturated aqueous NaCl solution (3×). The combined aqueous layers were extracted with Et₂O (3×) and the combined organic layers were dried (Na₂SO₄) and evaporated. The residue was dissolved in Et₂O (55 mL) and DBN (16 mL, 134.1 mmol) and a solution of iodine (11.4 g, 44.7 mmol) in Et₂O (55 mL) was added dropwise. After stirring for 15 min, a saturated aqueous NaHCO₃ solution was added and the layers were separated. The organic layer was dried and evaporated. The oil obtained was dissolved in C₆H₆ (55 mL) and DBN (16 mL) and stirred for 3 h at 130 °C. Upon cooling, the reaction mixture was added to a saturated aqueous Na₂S₂O₃ solution. The mixture was extracted with Et₂O (3×) and the organic layer was dried (Na₂SO₄) and evaporated. Purification of the residue by column chromatography (SiO₂, hexane) afforded (S)-**5g** (2.34 g, 84%) as a colorless oil. $[\alpha]_D^{24} -11.4^\circ$ (c 0.26, MeOH). ¹H NMR (400.13 MHz, CDCl₃) δ 4.69 (s, 1H), 4.67 (s, 1H), 2.69 (dd, *J* = 16.9, 3.3 Hz, 1H), 2.5–2.4 (m, 1H), 2.29 (t, *J* = 11.5 Hz, 1H), 2.2–2.1 (m, 2H), 1.9–1.8 (m, 1H), 1.89 (s, 3H), 1.68 (s, 3H), 1.54 (ddd, *J* = 19.2, 12.1, 10.5 Hz, 1H) ppm. ¹³C NMR (100.61 MHz, CDCl₃) δ 147.7, 137.4, 109.4, 95.9, 46.4, 43.9, 32.3, 28.8, 27.5, 20.6 ppm. MS *m/z* (%) 262 (M⁺, 45), 261 (22), 233 (23), 217 (44), 151 (30), 135 (70), 134 (24), 119 (29), 107 (85), 105 (45), 95 (65), 93 (100), 67 (97). HRMS calcd for C₁₀H₁₅I, 262.0219; found, 262.0223.

2.20. (+)-(4R)-2-Iodo-1-methyl-4-(prop-1-en-2-yl)-cyclohex-1-ene R-5g

According to the general procedure described above for the Barton reaction, ketone (R,R)-**4f** (1.0 g, 6.6 mmol) was treated with H₂NNH₂·H₂O (5.1 mL, 164.3 mmol) and Et₃N (1.8 mL, 13.1 mmol) in ethanol (18 mL), followed by DBN (7 mL, 59.1 mmol) and I₂ (5 g, 19.7 mmol) in Et₂O (21 mL), at 25 °C, and DBN (7 mL) in C₆H₆ (21 mL). Purification of the residue by column chromatogra-

phy (SiO₂, 100 hexane) afforded (*R*)-**5g** (1.18 g, 69%) as a colorless oil. $[\alpha]_D^{24} +11.9^\circ$ (c 0.25, MeOH). MS *m/z* (%) 262 (M⁺, 35), 218 (50), 217 (36), 151 (27), 135 (58), 134 (26), 119 (29), 107 (82), 105 (51), 95 (52), 93 (100), 79 (69). HRMS calcd for C₁₀H₁₅I, 262.0219; found, 262.0226.

2.21. Ethyl (–)-(2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-9-[(5*S*)-2-methyl-5-(prop-1-en-2-yl)-cyclohex-1-ene]nona-2,4,6,8-tetraenoate (*S*)-**7g**: general procedure for the Suzuki reaction

t-BuLi (0.32 mL, 1.7 M in hexane, 0.54 mmol) was added to a cold (–78 °C) suspension of **5g** (0.07 g, 0.26 mmol) in THF (1.0 mL). After stirring for 30 min, trimethyl borate (0.06 mL, 0.52 mmol) was added and the mixture was stirred for 1 h at 0 °C, and then heated to room temperature. Pd(PPh₃)₄ (0.024 g, 0.02 mmol), followed by iodide **9** [simultaneously generated by treating stannane **8** (0.1 g, 0.20 mmol) with a solution of I₂ in CH₂Cl₂] dissolved in THF (1.0 mL), were then added. After stirring for 10 min, a 10% aqueous TIOH solution was added (1.8 mL, 0.79 mmol), and the resulting mixture was stirred at 25 °C for 30 min. It was diluted with Et₂O (2.0 mL) and filtered through Celite. The filtrate was washed with a saturated aqueous NaHCO₃ solution (3×), dried (Na₂SO₄) and evaporated. The residue was purified by chromatography (SiO₂, 95:5 hexane/EtOAc) to afford (*S*)-**7g** (0.06 g, 87%) as yellow solid. $[\alpha]_D^{24} -48.0^\circ$ (c 0.014, MeOH). IR (NaCl) ν 1707 (s) cm⁻¹. ¹H NMR (400.13 MHz, (CD₃)₂CO) δ 7.31 (dd, *J* = 15.0, 11.5 Hz, 1H), 6.97 (d, *J* = 15.9 Hz, 1H), 6.92 (d, *J* = 15.9 Hz, 1H), 6.35 (d, *J* = 15.0 Hz, 1H), 6.15 (d, *J* = 11.5 Hz, 1H), 5.80 (s, 1H), 4.78 (s, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.6–2.4 (m, 1H), 2.35 (s, 3H), 2.3–2.0 (m, 4H), 2.05 (s, 3H), 1.81 (s, 3H), 1.8–1.7 (m, 1H), 1.5–1.4 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 2H) ppm. ¹³C NMR (100.61 MHz, (CD₃)₂CO) δ 168.2, 154.5, 151.6, 140.4, 137.1, 136.4, 131.9, 131.4, 130.5, 129.8, 123.7, 120.3, 110.3, 60.9, 43.3, 35.2, 32.6, 29.4, 22.2, 21.9, 20.3, 15.7, 14.8 ppm. UV (EtOH) λ_{max} 273, 362 nm. MS *m/z* (%) 410 (17), 332 (34), 205 (39), 159 (70), 132 (80), 131 (100), 117 (38), 91 (47). HRMS calcd for C₂₃H₃₂O₂, 340.2402; found, 340.2430.

2.22. Ethyl (+)-(2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-9-[(5*R*)-2-methyl-5-(prop-1-en-2-yl)-cyclohex-1-ene]nona-2,4,6,8-tetraenoate (*R*)-**7g**

According to the general procedure described above for the Suzuki reaction, iodide (*R*)-**5g** (0.07 g, 0.26 mmol) was treated with *n*-BuLi (0.32 mL, 1.7 M in hexane, 0.54 mmol), followed by B(OMe)₃ (0.06 mL, 0.52 mmol), and iodide **9** [previously generated from stannane **8** (0.10 g, 0.20 mmol)]. After stirring the mixture for 30 min at 25 °C, purification of the residue by column chromatography (SiO₂, 95:5 hexane/EtOAc) afforded (*R*)-**7g** (0.06 g, 84%) as a yellow oil. $[\alpha]_D^{24} +53.4^\circ$ (c 0.01, MeOH). MS *m/z* (%) 410 (17), 332 (34), 159 (50), 132 (30), 131 (100), 117 (38) HRMS calcd for C₂₃H₃₂O₂, 340.2402; found, 340.2420.

2.23. (–)-(2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-9-[(5*S*)-2-methyl-5-(prop-1-en-2-yl)-cyclohex-1-ene]nona-2,4,6,8-tetraenoic acid (*S*-**3g**)

According to the general procedure described above for the hydrolysis of esters, (*S*)-**7g** (0.06 g, 0.18 mmol) in ethanol (1 mL) was treated with a 5 M aqueous KOH solution (0.33 mL) and then refluxed for 30 min. Purification by chromatography (SiO₂, 95:5 CH₂Cl₂/MeOH), afforded 0.044 g of (*S*)-**3g** (82%) as a yellow solid. $[\alpha]_D^{24} -45.6^\circ$ (c 0.2, MeOH). IR (NaCl) ν 3100–2700 (br), 1671 (s) cm⁻¹. ¹H NMR (400.13 MHz, (CD₃)₂CO) δ 7.30 (dd, *J* = 15.0, 11.5 Hz, 1H), 6.96 (d, *J* = 15.7 Hz, 1H), 6.90 (d, *J* = 15.7 Hz, 1H), 6.34 (d, *J* = 15.0 Hz, 1H), 6.13 (d, *J* = 11.5 Hz, 1H), 5.82 (s, 1H), 4.76 (s, 2H), 2.5–2.3 (m, 1H), 2.32 (s, 3H), 2.4–2.0 (m, 4H), 2.05

(s, 3H), 1.85 (s, 3H), 1.79 (s, 3H), 1.5–1.4 (m, 1H), 0.96 (dd, *J* = 10.4, 6.8 Hz, 1H) ppm. ¹³C NMR (100.61 MHz, (CD₃)₂CO) δ 168.1, 153.8, 150.7, 139.4, 136.1, 135.6, 130.9, 130.5, 129.6, 128.9, 122.7, 119.3, 109.4, 42.3, 34.3, 31.7, 30.5, 21.3, 21.0, 19.4, 13.8 ppm. UV (EtOH) λ_{max} 270, 348 nm. MS *m/z* (%) 313 (21), 312 (100), 157 (45), 145 (49), 143 (34), 119 (45), 105 (57). HRMS calcd for C₂₁H₂₈O₂, 312.2089; found, 312.2089. Elem. Anal. Calcd for C₂₁H₂₈O₂: C, 80.73%; H, 9.03; found: C, 80.02%; H, 9.33.

2.24. (+)-(2*E*,4*E*,6*Z*,8*E*)-3,7-Dimethyl-9-[(5*R*)-2-methyl-5-(prop-1-en-2-yl)-cyclohex-1-ene]nona-2,4,6,8-tetraenoic acid (*R*-**3g**)

According to the general procedure described above for the hydrolysis of esters, (*R*)-**7g** (0.06 g, 0.17 mmol) in ethanol (1 mL) was treated with a 5 M aqueous KOH solution (0.33 mL) and then refluxed for 30 min. Purification by chromatography (SiO₂, 95:5 CH₂Cl₂/MeOH), afforded 0.041 g of (*R*)-**3g** (77%) as a yellow solid. $[\alpha]_D^{24} +43.8^\circ$ (c 0.12, MeOH). MS *m/z* (%) 313 (23), 312 (100), 157 (34), 145 (42), 143 (27), 119 (34), 105 (49). HRMS calcd for C₂₁H₂₈O₂, 312.2089; found, 312.2093. Elem. Anal. Calcd for C₂₂H₃₀O₂: C, 80.94%; H, 9.26%; found: C, 80.46%; H, 9.21.

2.25. Reporter cells

To generate RAR and RXR reporter cells HeLa cells were stably transfected with an (17m) 5- β -G-Luc-Neo reporter gene and with Gal4-mRAR α or Gal4-hRXR β plus Δ ABRXRdn plasmid. They were maintained in DMEM that contained 5% fetal calf serum (FCS) and gentamycin (40 mg/mL) supplemented with geneticin G418 (0.8 mg/mL), puromycin (0.3 mg/mL). Hygromycin (0.2 mg/mL) was added additionally only for the Gal4-hRXR β -engineered HeLa cell line.

2.26. Determination of RAR and RXR agonist and antagonist activities

The ligand-activation assays were performed in DMEM without red phenol with 5% FCS. To determine the RAR α , RAR β , RAR γ and RXR β induction potential of the ligands, equal amounts (13,000 cells/well) of the corresponding cell line were seeded in a 96-well plate. Cells were allowed to attach to the bottom and approximately 4–5 h later the ligands were added in respective wells with respective concentrations. The cells were incubated at 37 °C in 5% CO₂ for 16 h (overnight). After overnight incubation, the cells were washed (PBS) and lysed (50 μ L of lysis buffer: 25 mM Tris phosphate (pH 7.8), 2 mM EDTA, 1 mM DTT, 10% glycerol, and 1% Triton X-100) for 15 min. Equal aliquots (25 μ L) of the cell lysates were transferred to an opaque white Optiplate-96 well plate and the luminescence in RLU (relative luminescence units) was determined on a MicroLumat LB96P luminometer (Berthold) after automatic injection of 50 μ L of luciferin buffer (20 mM Tris phosphate (pH 7.8), 1.07 mM MgCl₂, 2.67 mM MgSO₄, 0.1 mM EDTA, 33.3 mM DTT) including 0.53 mM ATP, 0.47 mM luciferin, and 0.27 mM coenzyme A. The receptor activation potential of each ligand was presented as fold induction measured as ratio of RLU of the compound over the RLU of the vehicle control.

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- Although the lithium anion at the α' position of **5b** could be formed using instead MeLi, the subsequent trapping with tri-isopropylborate was very slow, and only protonation was observed upon work-up.