Novel (2*E*,4*E*,6*Z*)-7-(2-Alkoxy-3,5-dialkylbenzene)-3-methylocta-2,4,6-trienoic Acid Retinoid X Receptor Modulators Are Active in Models of Type 2 Diabetes

P. Y. Michellys,*[,§] R. J. Ardecky,[§] J. H. Chen,[§] D. L. Crombie,[Δ,⊥] G. J. Etgen,[▽] M. M. Faul,[‡] A. L. Faulkner,[§,||] T. A. Grese,[†] R. A. Heyman,[∞] D. S. Karanewsky,[§,⊗] K. Klausing,[+] M. D. Leibowitz,[Δ] S. Liu,[Δ] D. A. Mais,[#] C. M. Mapes,[§] K. B. Marschke,[#] A. Reifel-Miller,[▽] K. M. Ogilvie,[Δ,◆] D. Rungta,[#] A. W. Thompson,[§,●] J. S. Tyhonas,[§] and M. F. Boehm[§,⊥]

Department of Medicinal Chemistry, Ligand Pharmaceuticals, Incorporated, 10275 Science Center Drive, San Diego, California 92121

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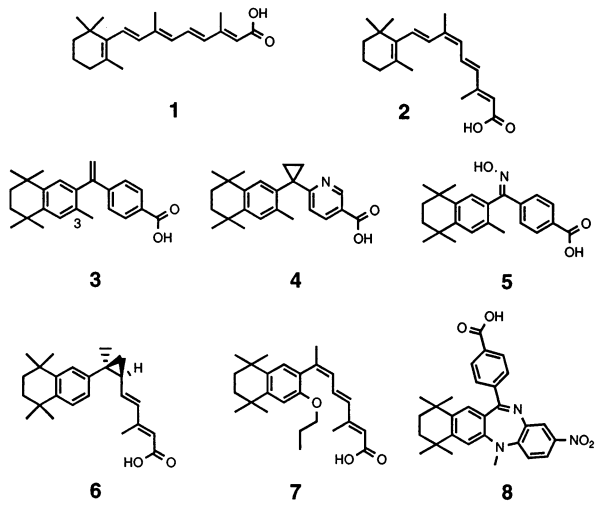
Previous data have shown that RXR-selective agonists (e.g., **3** and **4**) are insulin sensitizers in rodent models of non-insulin-dependent diabetes mellitus (NIDDM). Unfortunately, they also produce dramatic increases in triglycerides and profound suppression of the thyroid hormone axis. Here we describe the design and synthesis of new RXR modulators that retain the insulin-sensitizing activity of RXR agonists but produce substantially reduced side effects. These molecules bind selectively and with high affinity to RXR and, unlike RXR agonists, do not activate RXR homodimers. To further evaluate the antidiabetic activity of these RXR modulators, we have designed a concise and systematic structure−activity relationship around the *2E*,4*E*,6*Z*-7-aryl-3-methylocta-2,4,6-trienoic acid scaffold. Selected compounds have been evaluated using insulin-resistant rodents (*db*/*db* mice) to characterize effects on glucose homeostasis. Our studies demonstrate the effectiveness of RXR modulators in lowering plasma glucose in the *db*/*db* mouse model.

Introduction

Retinoids are of considerable therapeutic interest as evidenced by the many drugs from this class that are currently marketed for diseases such as acne, psoriasis, Kaposi's sarcoma, cutaneous T-cell lymphoma (CTCL), and various cutaneous disorders of keratinization.[1−4] The molecular targets of retinoids are two families of homologous receptors: the retinoic acid receptors (RARs) and the retinoid x receptors (RXRs). These receptors are members of the intracellular nuclear receptor superfamily,[5] which function to regulate gene transcription. Both RARs and RXRs are further divided into three receptor subtypes, α, *β*, and *γ*, each encoded by a single gene.[6] All-*trans*-retinoic acid (ATRA, **1**) is the endogenous low-molecular weight ligand that modulates the transcriptional activity of the RARs, whereas 9-*cis*-retinoic acid (9-*cis*-RA, **2**) is the endogenous ligand of RXRs (Chart 1).[7,8]

Chart 1



Recently, a new drug targeting RXRs has emerged. Methyl-4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)ethenyl]-benzoate (LGD1069, **3**) is an RXR agonist,[9] which is administered for the treatment of CTCL[10−12] and is currently in clinical trials for non-small cell lung cancer.[13] This compound is a member of the series of RXR agonists, which include compounds such as **4** (LG100268) and **5** (Chart 1).[14−16]

Structural features of these molecules include a *p*-benzoic acid linked to a 5,6,7,8-tetramethyl-5,5,8,8-tetrahydronaphthyl moiety via a substituted methylene bridge. Structure−activity relationship (SAR) studies have revealed the critical importance of the 3 position within such molecules. It has been found that any small

* To whom correspondence should be addressed. E-mail: pmichellys@ligand.com
§ Department of Medicinal Chemistry, Ligand Pharmaceuticals, Inc., San Diego, CA.
Δ Department of Pharmacology, Ligand Pharmaceuticals, Inc., San Diego, CA.
⊥ Current address: Conforma Therapeutics, San Diego, CA.
|| Current address: Procter and Gamble, Cincinnati, OH.
▽ Division of Endocrine Research, Lilly Research Laboratories, Indianapolis, IN.
‡ Process Chemistry Research, Lilly Research Laboratories, Indianapolis, IN.
† Discovery Chemistry Research, Lilly Research Laboratories, Indianapolis, IN.
# Department of New Leads Discovery, Ligand Pharmaceuticals, Inc., San Diego, CA.
∞ Current address: X-Ceptor Therapeutics, San Diego, CA.
+ Department of Molecular and Cell Biology, Ligand Pharmaceuticals Inc., San Diego, CA.
◆ Current address: Pfizer Inc., San Diego, CA.
⊗ Current address, Genomics Institute of Norvartis Research Foundation, San Diego, CA.
● Current address: Roche Bioscience, Palo Alto, CA.

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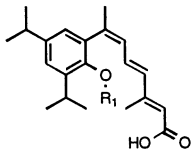
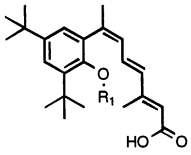
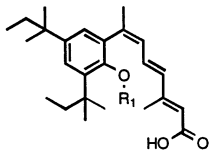
Chart 2



R_1 = Methyl, **11a**
R_1 = Ethyl, **11b**
R_1 = 2-fluoroethyl, **11c**
R_1 = 2,2-difluoroethyl, **11d**
R_1 = 2,2,2-trifluoroethyl, **11e**
R_1 = Propyl, **11f**
R_1 = Butyl, **11g**



R_1 = Methyl, **12a**
R_1 = Ethyl, **12b**
R_1 = 2,2-difluoroethyl, **12c**
R_1 = 2,2,2-trifluoroethyl, **12d**
R_1 = Propyl, **12e**



R_1 = Methyl, **13a**
R_1 = Ethyl, **13b**
R_1 = 2,2-difluoroethyl, **13c**
R_1 = Propyl, **13d**

substitution in the 3 position (Chart 1) will increase RXR selectivity by introducing conformational restrictions to the molecule. These results have been rationalized using molecular modeling.[9] Further exploration of the SAR has led to the replacement of the *exo* olefin present in **3** with a cyclopropyl (**4**) or an oxime (**5**).[15,16] These substitutions slightly change the torsional angle of the two aromatic rings, which in turn leads to an increase in their RXR potency and selectivity.

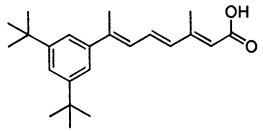
Mode of Action

RXRs function to regulate transcription either as homodimers (RXR:RXR) or as heterodimers with other nuclear receptors such as RARs, thyroid hormone receptor (TR), vitamin D receptor (VDR), liver X receptor (LXR), farnesoyl X receptor (FXR), peroxisome proliferator-activated receptors (PPARs), and nerve growth factor-induced receptor (NGFIB).[6,17] It has been demonstrated that for RXR:RAR, RXR:VDR, and RXR:TR heterodimers, an RXR agonist will not activate the heterodimer without the corresponding ligand for the heterodimeric partner (nonpermissive heterodimers). However, for other heterodimers such as RXR:PPARs, RXR:LXR, RXR:FXR, and RXR:NGFIB, a ligand for either or both of the heterodimer partners may serve to activate the heterodimeric complex (permissive heterodimers). As a result, the presence of ligands for both partners can lead to an additive or synergistic activation of the heterodimer, or both.[17]

Because of this unique capability to interact with a variety of other nuclear receptors, RXRs are very attractive targets for drug discovery.[18] We discuss the advantages of a novel series of RXR ligands, which exhibit heterodimer selectivity. Because these RXR ligands activate specific heterodimers, we refer to the compounds as selective RXR modulators. For the series of compounds described herein, the focus will be on the RXR:PPARγ heterodimer.

RXR:PPAR heterodimers play a major role in the regulation of both glucose (RXR:PPARγ) and lipid (RXR:PPARα) metabolism.[19−22] Recent reports have shown that synthetic RXR agonists (rexinoids) such as **3**, **4**, and **6** are insulin-sensitizing agents[23] and are capable of decreasing hyperglycemia and hyperinsulinemia.[17,24,25] Unfortunately, RXR agonists also produce various side effects including a dramatic increase of triglycerides and a suppression of the thyroid hormone axis.[24] This undesirable side effect profile prevents their use as chronic therapies for type 2 diabetic patients. More recently, it was reported that RXR homodimer antagonists such as **7** and **8** (Chart 1) affect glucose homeostasis in an animal model.[26, 27]

Chart 3



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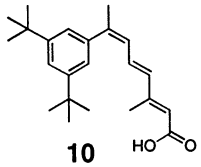

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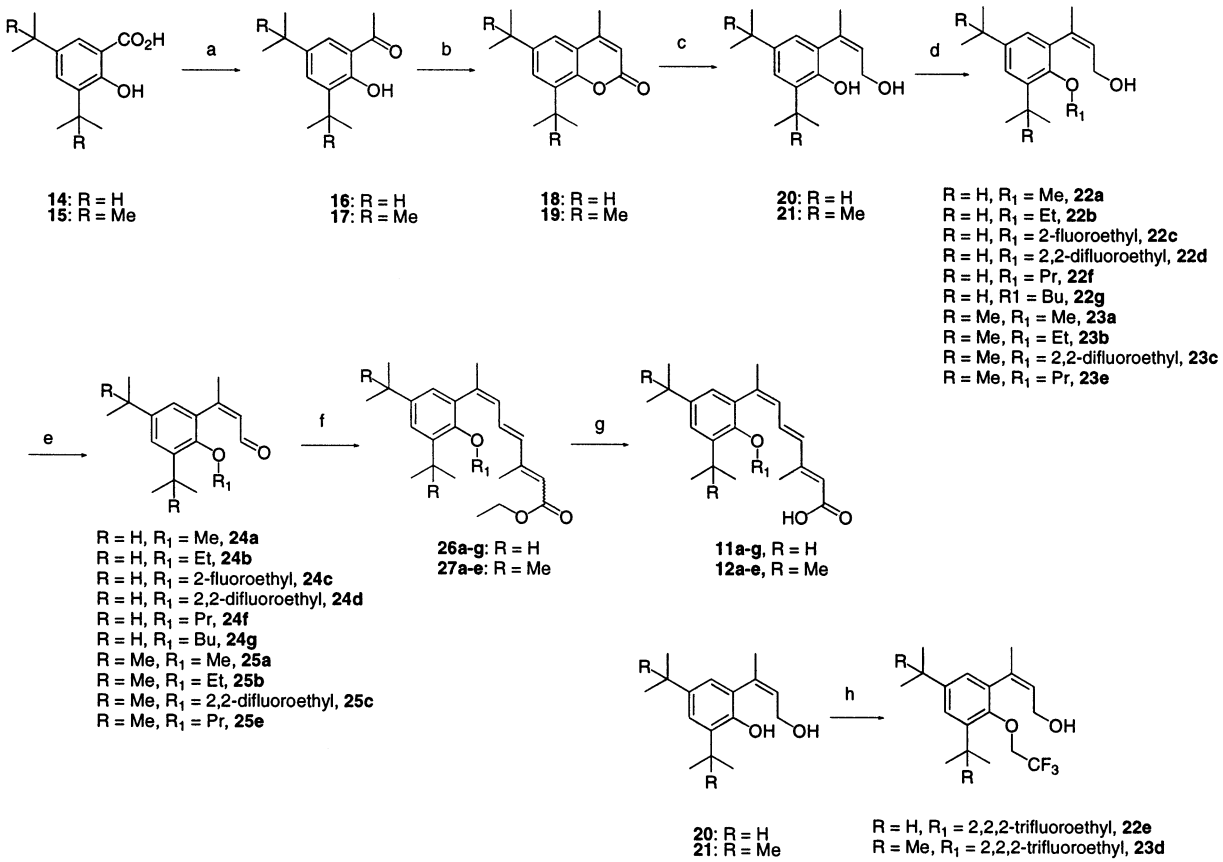
Chemistry

The new modulators we describe are based on the (2*E*,4*E*,6*Z*)-7-(2-alkoxy-3,5-di-alkylbenzene)-3-methylocta-2,4,6-trienoic acid scaffolds **11**, **12**, and **13** (Chart 2). Previous SAR investigation of structurally similar molecules led to the discovery of very potent trienoic acids derivatives, **9** (ALRT1550) and **10** (Chart 3), respectively (2*E*,4*E*,6*E*)-7-(3,5-di-*tert*-butylphenyl)-3-methyl-octa-2,4,6-trienoic acid and (2*E*,4*E*,6*Z*)-7-(3,5-di-*tert*-butylphenyl)-3-methyl-octa-2,4,6-trienoic acid.[28] **9** is an RAR agonist, whereas **10** is a pan-agonist whose activity is essentially identical to that of 9-*cis*-retinoic acid. The receptor selectivity of these compounds is undoubtedly determined by the configuration of the C-6 olefin bond precisely; the presence of the 6*E* olefin favors RAR selectivity, whereas the presence of the 6*Z* olefin induces RXR selectivity (pattern observed with all-*trans*-retinoic acid **1** and 9-*cis*-retinoic acid **2**).

As evidenced by their high potency and selectivity, these molecules were very interesting as a starting point for SAR studies. We have used these templates to design and synthesize more selective RXR modulators than those modulators previously described (Chart 2).

Conversion of the salicylic acids **14** and **15** into the corresponding acetylphenols **16** and **17** using 3 equiv of MeLi in THF at 0 °C was accomplished in good yield (>75%).[29] Treatment of **16** and **17** in refluxing toluene with an excess (2.5 equiv) of ethyl(triphenylphosphoranilidene)acetate afforded the coumarins **18** and **19** in good yield (>85%).[30] This particular coumarin synthesis is the most convenient and consistent route to these structures that we have found so far.[31,32] The sequence is consistently effective independent of scale (milligrams to multigrams). Reduction of **18** and **19** with LAH or $NaAlH_4$ in ether at 0 °C gives the corresponding phenolic alcohols **20** and **21** in quantitative yield without alteration of the established double bond. Introduction of the alkoxy side chain is achieved by selective alkylation of the phenol using Cs_2CO_3 in DMF

Scheme 1. Synthetic Scheme for the Synthesis of Compounds **11a**−**g** and **12a**−**e**[a]



[a] Reagents and conditions: (a) MeLi, THF, −78 °C to rt; (b) ethyl (triphenylphosphoranilidene)acetate, toluene, reflux; (c) $NaAlH_4$, ether, 0 °C; (d) R_1−Br, Cs_2CO_3, DMF; (e) TPAP, NMO, CH_2Cl_2; (f) triethyl-3-methylphosphonocrotonate, *n*-BuLi, THF−DMPU, −78 °C to rt; (g) 2 N aq LiOH, MeOH, THF reflux, then HCl and recrystallization from CH_3CN; (h) 1-bromo-2,2,2-trifluoroethane, Cs_2CO_3, DMF, 50 °C, sealed tube, 16 h.

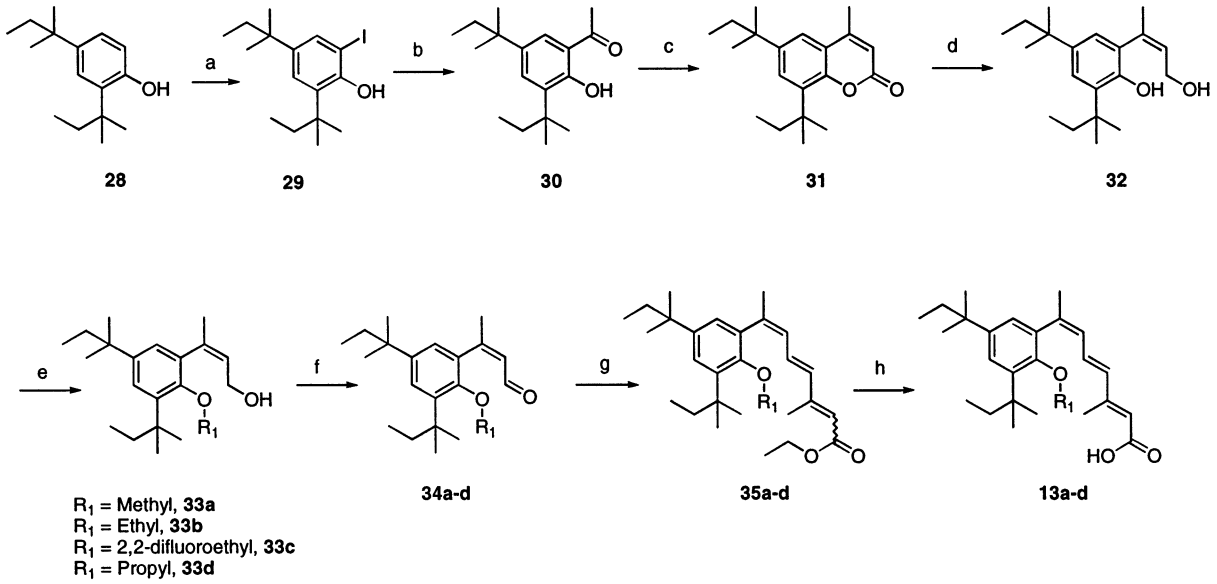
at room temperature to afford **22a**−**g** and **23a**−**e**. These conditions were effective except for the introduction of the 2,2,2-trifluoroethoxy group. In this case, because of the high volatility and reduced reactivity of the 2-bromo-1,1,1-trifluoroethane, the reaction was conducted into a sealed tube at 50 °C. Oxidation of the resultant allylic alcohols **22a**−**g** and **23a**−**e** with a catalytic amount (5−10%) of tetrapropylammonium perruthenate (TPAP)[33,34] and an excess of NMO (1.5 equiv) in methylene chloride yields the corresponding unsaturated aldehydes **24a**−**g** and **25a**−**e** in quantitative yield. The aldehydes **24a**−**g** and **25a**−**e** are directly subjected to a Horner−Wadsworth−Emmons reaction with the anion of triethyl-3-methylphosphonocrotonate (prepared by slow addition of *n*-BuLi to a solution of triethyl phosphonocrotonate in THF−DMPU at −78 °C)[28,30,35−37] to afford in excellent overall yield (>85%, two steps) the corresponding esters **26a**−**g** and **27a**−**e**. Hydrolysis of these esters with 2 N aqueous LiOH in refluxing THF−MeOH (or, alternatively, aqueous 5 N KOH in refluxing ethanol) affords the crude corresponding trienoic acids **11a**−**g** and **12a**−**e**. Recrystallization of these crude acids from acetonitrile affords the desired pure (2*E*,4*E*,6*Z*)-trienoic acids **11a**−**g** and **12a**−**e** in good yield and excellent isomeric purity (>99%).

Scheme 2 mirrors Scheme 1 in all respects except for the method used for the synthesis of the acetylphenol **30**. This alteration resulted from the lack of a commercial source for 3,5-di-*tert*-amyl salicylic acid. The acetyl moiety is introduced via addition of *N*,*N*-dimethylacetamide to the dianion of **29**.[38] The iodophenol **29** was obtained from the iodination of the inexpensive 2,4-di-*tert*-amylphenol **28** with a slight excess (1.1 equiv) of *N*-iodosuccinimide and a catalytic amount (10%) of TsOH in methylene chloride. Treatment of the 6-iodo-2,4-di-*tert*-amylphenol **29** with 2.5 equiv of *n*-BuLi in ether at −78 °C, followed by addition of an excess of *N*,*N*-dimethylacetamide, affords the corresponding acetylphenol **30**, typically isolated in 30−40% yield. Once compound **30** is obtained, its transformation into series **13a**−**d** was completed using the conditions depicted in Scheme 1. All yields are comparative, and we once again obtain the final trienoic acids (**13a**−**d**) as single isomers by recrystallization from acetonitrile.

Results

Biological Data. The binding of each compound to RXRα and RARγ has been characterized using ^{3}[H]-9-*cis*-RA for RXR and ^{3}[H]-ATRA for RAR (data shown as K_i). The RXR homodimer transcriptional activation profile of each compound was determined in CV-1 cells (using an AOX response element as the reporter), with the efficacy being measured relative to ATRA. The RXR activation profiles of RXR:RAR and RXR:PPARγ heterodimers were also determined in CV-1 cells. **4** and compounds with short alkoxy side chains (**11a**, **11b**, **12a**) are full agonists of the RXR homodimer and both RXR:RAR and RXR:PPARγ heterodimers. As the alkoxy side chain is lengthened, both cotransfection activities decrease (**11g**, **12c**). However, when tested in combina-

Scheme 2. Synthetic Scheme for the Synthesis of Compounds **13a**−**d**[a]



[a] Reagents and conditions: (a) NIS, TsOH, CH_2Cl_2; (b) *n*-BuLi, Et_2O, −78 °C, then DMA; (c) ethyl(triphenylphosphoranilidene)acetate, toluene, reflux; (d) $NaAlH_4$, ether, 0 °C; (e) R_1-X, Cs_2CO_3, DMF; (f) TPAP, NMO, CH_2Cl_2; (g) triethyl-3-methylphosphonocrotonate, *n*BuLi, THF−DMPU, −78 °C to rt; (h) 2 N aq LiOH, MeOH, THF reflux, then HCl and recrystallization from CH_3CN.

Table 1. In Vitro Profiling of Compounds **11a**−**g**, **12a**−**e**, and **13a**−**d**[a]

entries	compounds	RXRα K_i	RXRα agonist efficacy	RXRα agonist EC_{50}	RXRα antagonist efficacy	RXRα antagonist IC_{50}	RXR:PPARγ synergy efficacy	RXR:PPARγ synergy EC_{50}	RARγ K_i	RXR/RAR synergy (fold)
1	**4**	18 ± 1	70 ± 21	11 ± 10	12	NC	166 ± 57	38 ± 20	10000	7
2	**BRL49653**	NB	1 ± 1	NA	NA	NA	NA	NA	10000	NA
3	**11a**	1 ± 2	83 ± 19	2 ± 1	0	NA	324 ± 55	8 ± 5	10000	10
4	**11b**	2 ± 2	58 ± 18	2 ± 1	7 ± 8	NA	146 ± 44	1 ± 1	10000	5
5	**11c**	1 ± 0	43 ± 4	7 ± 1	17 ± 23	4 ± 3	129 ± 9	4 ± 2	10000	4
6	**11d**	2 ± 1	11 ± 1	NC	65 ± 5	1 ± 1	91 ± 31	10 ± 1	10000	3
7	**11e**	3 ± 2	3 ± 2	NC	87 ± 2	6 ± 4	70 ± 23	3 ± 1	1860	2
8	**11f**	3 ± 3	4 ± 1	NC	85 ± 4	4 ± 3	62 ±16	5 ± 4	10000	2
9	**11g**	4 ± 5	2 ± 2	NC	91 ±4	4 ± 3	39 ± 17	12 ± 9	10000	1
10	**12a**	1 ±1	65 ± 12	36 ± 15	5 ± 7	NA	180 ± 55	7 ± 3	10000	3
11	**12b**	11 ± 10	12 ± 6	18 ± 12	61 ± 10	8 ± 6	70 ± 19	2 ± 2	10000	3
12	**12c**	3 ± 2	4 ± 2	NC	84 ±10	8 ± 4	60 ± 29	3 ± 1	10000	2
13	**12d**	27 ± 14	1 ± 0	NC	93 ± 3	8 ± 4	40 ± 3	2 ± 2	4028	1
14	**12e**	14 ± 7	9 ± 6	NC	74 ± 1	43 ± 12	80 ± 37	154 ± 60	10000	1
15	**13a**	2 ± 1	35 ± 15	506 ± 50	15 ± 21	NA	140 ± 46	6 ± 1	10000	2
16	**13b**	2 ± 1	11 ± 5	NC	72 ± 2	17 ± 5	129 ± 2	9 ± 4	2503	2
17	**13c**	29 ± 5	2 ± 1	NC	90 ± 2	16 ± 10	69 ± 16	11 ± 3	10000	1
18	**13d**	23 ± 6	5 ± 2	NC	88 ± 1	13 ± 2	58 ± 10	19 ± 5	10000	1

[a] K_i, EC_{50}, and IC_{50} are expressed in nM. RXR: RAR synergy is expressed as fold induction above an EC_{30} concentration of TTNPB. NB: No Binding; NA: Not Applicable.

tion with 100 nM BRL49653 (Rosiglitazone), the modulators produce substantial activation of RXR:PPARγ heterodimers. The same protocol was used to further characterize the acids **11a**−**g**, **12a**−**e**, and **13a**−**d**. Results are summarized in Table 1.

All the compounds bind with high affinity to RXRα ($1 < K_i < 29$ nM) independent of the size of the alkoxy side chain. No high-affinity RARγ binding is observed; only **11e**, **12d**, and **13b** bind weakly to RARγ (1860, 4028, and 2503 nM respectively; entries 7, 13, and 16). As expected, short alkoxy side chains (e.g., methoxy, **11a**, **12a**, and ethoxy, **11b**) show excellent RXR homodimer agonist activity (efficacy > 58% and $EC_{50} < 19$ nM; Table 1, entries 3, 4, and 10 respectively) except compound **13a** that has a partial agonist profile (see Table 1, entry 15). When the alkoxy chain becomes longer, RXR homodimer agonist activity slowly decreases and disappears entirely when $R_1 = C_3H_7$ (**11f**, **11g**, **12e**, and **13d**), with the exception of the 2,2-difluoroethoxy and 2,2,2-trifluoroethoxy side chain (**11e**, **12c**, **12d**, and **13c**; Table 1, entries 7, 12, 13, and 17 respectively). These appear to be intermediate between ethyl and propyl in activity as would be expected on the basis of steric arguments. Fluorines are not only very well tolerated but also allow a very smooth transition from agonist to partial agonist to antagonist activity (see Table 1, entries 5−7).

Cotransfection activities of selected RXR modulators in RXR homodimer agonist mode (Figure 1), RXR homodimer antagonist mode (Figure 2), and RXR:PPARγ heterodimer synergy mode (Figure 3) are shown.

RXR agonists show a dramatic synergistic response when tested in combination with BRL49653 (Table 1, entries 1, 3, and 10). Evaluation of these compounds for their RXR:PPARγ heterodimer activity showed the expected activity for the RXR agonists **11a**, **12a**, and

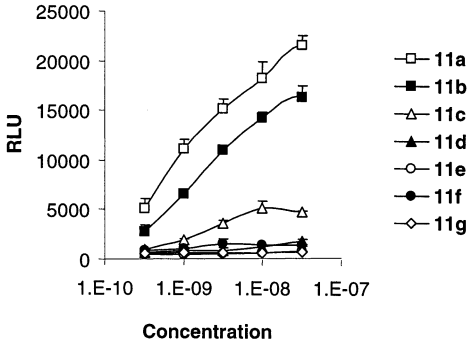


Figure 1. RXRα cotransfection data (agonist mode) of compounds **11a**−**g**.

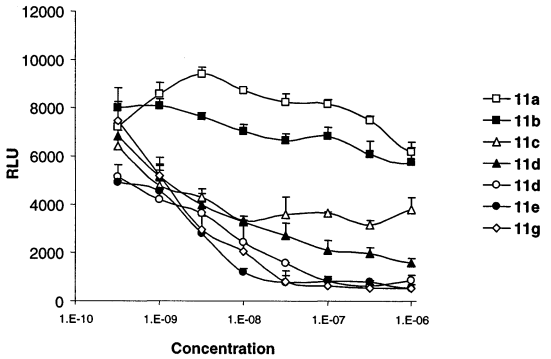


Figure 2. RXRα cotransfection data (antagonist mode) of compounds **11a**−**g**.

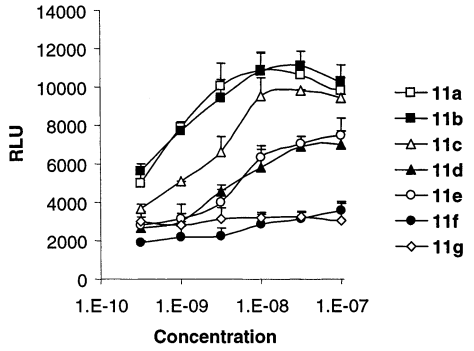


Figure 3. RXRα:PPARγ cotransfection assay of compounds **11a**−**g** in synergy mode with 100 nM of **BRL 49653**.

11b. However, measurement of RXR/PPARγ activity proved to be more difficult for the RXR homodimer modulators because they exhibit a concomitant decrease in the RXR:PPARγ heterodimer activity when administered alone (data not shown). However, when the RXR homodimer modulator and 100 nM BRL49653 were used in combination, a much cleaner response and a larger window of activity was observed. Responses ranging from good to moderate are observed with the modulators.

A similar activity profile was observed on the RXR:RAR heterodimer. Synergy was observed when RXR agonists were tested in combination with the potent RAR agonist TTNPB. To assess the potential of the described RXR modulators to synergize with RAR agonists, we have developed an in vitro RXR:RAR synergy assay using a combination of 3 nM TTNPB with the test compounds. The RXR agonists and modulators (**4**, **11a**, **11b**, **11c**, **12a**, and **13a**; Table 1, entries 1, 3, 4, 5, and 10) all show a synergistic response (7-, 10-, 5-, 4-, and 3-fold induction respectively). However, as the side chain is lengthened, the RXR:RAR synergy activity progressively decreases and is absent (equal or less than 2-fold induction) for full RXR antagonists (Table 1, entries 7, 8, 9, 12, 13, 14, 17, and 18). More interestingly, it appears that the RXR:RAR synergy is not only related to the length of the alkoxy side chain but can also be modulated by using a combination of the side chain and the aromatic ring substitutions. More precisely, when bulkier aromatic substitution is used for a given alkoxy side chain, a decrease of RXR:RAR synergy is observed. As an example, when the ring substituents increase in size (di-*iso*-propyl, di-*tert*-butyl, and di-*tert*-amyl, respectively), synergy decreases from 3-fold to 2- and 1-fold (Table 1, entries 6, 12, and 17) for compounds **11d**, **12c**, and **13c**, respectively.

Table 2. In Vivo Activity of Selected RXR Modulators[a,b,c]

compounds	lean control[d]	*db*/*db* control[d]	drug-treated *db*/*db*[d]	% normalization vs **BRL46953**
BRL 49653	205 ± 5	750 ± 15	412 ± 10	100
4	207 ± 5	740 ± 15	400 ± 5	101
11g	203 ± 5	750 ± 15	502 ± 7	33
12b	200 ± 5	748 ± 15	412 ± 10	100
12c	203 ± 5	749 ± 10	409 ± 6	101

[a] Hypoglycemic activity of selected RXR modulators **11g**, **12b**, and **12c** in the *db*/*db* mouse model after 7 days of dosing. [b] FA: compound used as the free acid; Na Salt: compound used as the sodium salt. [c] **BRL49653** used as reference compound for efficacy (100%). [d] In mg/dL.

In Vivo Evaluation. The ability of these compounds to lower plasma glucose was evaluated in the *db*/*db* mouse. These mice have a leptin receptor defect rendering them progressively obese, hyperglycemic, and hypertriglyceridemic with age and are commonly used as a model of type 2 diabetes. BRL49653 and **4** served as positive controls for glucose-lowering efficacy in these experiments, and the data were compared both to a vehicle-treated group of *db*/*db* animals and to a group of age-matched lean littermates. Each RXR modulator was given orally as a single agent (as the Na salt to enhance their solubility, except **12c**) at 30 mg/kg/day. **4** (10 mg/kg/day) was used as the free acid. BRL49653 was used at 10 mg/kg/day. The data collected are shown in Table 2.

After seven days of treatment, **4** shows very good glucose-lowering activity and is as efficacious as BRL 49653 that typically gives 55% glucose reduction in our hands. The compound **12b**, which has some residual RXR homodimer activity (Table 1, entry 11), shows the same efficacy profile (i.e., same efficacy as BRL49653), whereas **11g** (LG101392), which has no RXR homodimer activity, shows only a partial efficacy in lowering glucose. However, **12c** (LG101506), where the butoxy side chain of **11g** is replaced with a 2,2-difluoroethoxy, shows a remarkable ability to lower glucose in these animals at 30 mg/kg (single daily dose) as the free acid (as good as BRL49653). These compounds achieve maximal plasma concentration 1 h after an oral dose (unpublished data). During our *db*/*db* mouse studies, plasma drug concentrations were measured 1 h after the final dose. Compound **12c** produced a higher drug concentration than **11g** (3.50 ± 0.93 μg/mL vs 2.10 ± 0.78 μg/mL). This increase in drug concentration is

Table 3. Side Effect Profile of Selected RXR Modulators[a]

compounds	control	**BRL 49653**	**4**	**12b**	**12c**	**11g**
triglycerides (mg/dL)	72 ± 10	78 ± 5	152 ± 10	92 ± 7	75 ± 5	63 ± 3
T4 (ng/mL)	73 ± 4	70 ± 3	37 ± 2	25 ± 4	70 ± 5	72 ± 5

[a] Effects of triglycerides and T4 levels on selected RXR modulators (**4**, **11g**, **12b**, and **12c**) in male Sprague−Dawley rats at 24 h.

Table 4. RXR:LXR Activity of Selected RXR Modulators[a]

compounds	**4**	**12b**	**12c**	**11g**
RXR:LXR activation (fold)	6.30 ± 0.53	2.04 ± 0.31	1.20 ± 0.15	0.60 ± 0.12

[a] RXR:LXR heterodimer cotransfection data. Data given in fold elevation above DMSO background in CV-1 cells at 1 μM.

presumably a major factor responsible for the difference in the ability of the compounds to lower plasma glucose.

Side effects (triglycerides and T4 levels) were evaluated in the Sprague−Dawley rat, which is a more sensitive model than the *db*/*db* mouse for triglycerides and thyroid axis effects.[39] Data for triglycerides and T4 were collected following administration of a single oral dose (30 mg/kg) to naïve animals. Triglycerides and T4 levels were measured at 2 and 24 h post dose, respectively. Results collected at 24 h are shown in Table 3. Again, **4** and **12b** raise triglycerides substantially. However, at the same dose, none of the RXR modulators tested elevate triglycerides. In a separate series of studies where Sprague−Dawley rats were dosed with **12c** for seven days (1, 3, 10, or 30 mg/kg/day), triglycerides were not evelevated at any time by any dose, whereas in these same experiments, **4** consistently produced elevated triglycerides at all times (data not shown). T4 levels were measured in the animals treated with a single oral dose of compound. Both **4** and **12b** cause a significant decrease in T4 levels (2.2-fold). However, neither **11g** nor **12c** reduce T4 levels. It is remarkable that **12c**, which shows the same efficacy on the glucose endpoint as either BRL49653 or **4**, did not raise triglycerides nor decrease T4 levels in Sprague−Dawley rats, thus overcoming two of the physiological side effects associated with RXR agonists.

Activation of the RXR:LXR heterodimer has been shown to produce elevations of triglycerides.[40] As a general trend, we found that RXR:LXR activation correlates with RXR:RXR homodimer activation. Table 4 shows the cotransfection data of **4**, **12b**, **12c**, and **11g** on the RXR:LXR heterodimer. Compound **4** strongly activates RXR:LXR (6.30-fold), compound **12b** moderately activates RXR:LXR (2.04-fold), and **12c** or **11g** does not activate the RXR:LXR heterodimer (1.20 and 0.60-fold respectively). However, whereas **4** dramatically elevates triglycerides, none of the other three compounds has any effect on triglycerides in Sprague−Dawley rats, although **12b** is a weak activator of the RXR:LXR heterodimer. These results demonstrate that in vitro activation of the RXR:LXR heterodimer does not necessarily result in elevation of triglycerides in vivo.

Discussion

Previously published results have demonstrated the utility of similar molecules possessing a trienoic acid moiety. These studies first indicated the ability of the alkoxy side chain to modulate the RXR homodimer cotransfection activity of such molecules while still maintaining comparable RXR binding.[41] However, these compounds undesirably activate the RXR:RAR heterodimer.[17,41−43] The studies described in this communication were focused on identifying RXR ligands deprived of RXR:RAR heterodimer activity or synergy.[44] This was realized by identifying a novel pharmacophore, namely (2*E*,4*E*,6*Z*)-7-(2-alkoxy-3,5-di-alkylbenzene)-3-methylocta-2,4,6-trienoic acid and by tuning the alkoxy side chain. To facilitate this SAR exploration, a quick and efficient synthetic strategy was developed. Through the course of these SAR studies, we have found that the size of the alkoxy side chain directly influences the biological activity of the molecules. By varying the size of the alkoxy side chain installed during the phenol protection steps (**20** and **21** to **22a**−**g** and **23a**−**e**, respectively, in Scheme 1 and **32** to **33a**−**d** in Scheme 2), we were able to construct analogues that demonstrated the in vitro profile of various RXR modulators (more precisely, RXR agonists, partial agonists, and antagonists). As a generalized rule, we have found that as the chain size increases, the agonist characteristic of the molecule decreases. In other words, a short alkoxy chain leads to an RXR agonist, whereas a long alkoxy chain will produce an antagonist. This dramatic change in activity is likely due to the alkoxy side chain, which may interfere with the correct folding of helix 12. Similar effects have been observed in other nuclear receptors such as the ER, where antagonists block the folding of helix 12 over the ligand-binding domain.[45] In addition, we have uncovered a delicate interplay between the steric bulk of the other aryl substituents and the alkoxy moiety, which allows for additional fine tuning of this effect.

Conclusion

In conclusion, we have described the synthesis and biological evaluation of a novel series of RXR modulators **11**, **12**, and **13**. These molecules possess the ability to selectively bind to RXR over RAR and to activate the RXR:PPARγ heterodimer in a selective manner. This new series was produced using a simple and efficient synthetic process that works well for either small- or large-scale synthesis. Through our SAR efforts, we have demonstrated the ability to smoothly transition between RXR agonists and RXR antagonists in a stepwise and predictable manner without altering the binding affinity of these molecules for RXR. Furthermore, we have demonstrated that the presence of fluorine in the alkoxy side chain appears to have a major effect on the in vivo efficacy of these compounds. This phenomenon may be due to increased solubility, which in turn affects the overall bioavailability of the fluorinated analogues. During experiments conducted in vivo, we have demonstrated that this series has the ability to lower glucose in the *db*/*db* mouse model (oral administration at 30 mg/kg/day). In a select subset of this series, this activity rivals that of currently available TZDs (e.g., BRL49653). One such compound, **12c**, when tested as the free acid,

is as efficacious at 30 mg/kg/day as are **4** or BRL49653 (both dosed at 10 mg/kg/day). When tested in the Sprague−Dawley rat, this series of RXR modulators neither raises triglycerides, nor suppresses the thyroid hormone axis, whereas agonists such as **4** produce both undesirable side effects.

Moreover, these RXR modulators, including **12c**, do not show any significant RXR: RAR synergy activity (<2-fold activation). In summary, **12c** is a new RXR modulator that exhibits promising activity in in vivo models of type 2 diabetes.

Experimental Section

General Experimental Chemical Procedures. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Brüker AC 400 or a Varian VXR 500 S spectrometer. Melting points were taken on an Electrothermal IA9100 Digital apparatus and are uncorrected. Mass spectra were taken on a Gilson 215 LC−MS apparatus. "Brine" refers to a saturated aqueous solution of NaCl. Unless otherwise specified, solutions of common inorganic salts used in workups are aqueous solutions. All moisture-sensitive reactions were carried out using oven-dried or flame-dried round-bottomed flasks and glassware under an atmosphere of dry nitrogen. All reagents and solvents were used without further purification unless otherwise noted. Most reactions were monitored by thin-layer chromatography (TLC) using a Merck TLC glass plate precoated with silica gel F254 (0.2 mm thick). Flash chromatography was performed using Merck silica gel 60.

General Procedure for the Synthesis of the Sodium Salt of the Acids 11, 12, and 13. The desired acid was introduced into a round-bottomed flask and diluted in dry dioxane (5 mL/mmol of acid). When the acid was completely dissolved, an equimolar quantity of volumetric 1 N NaOH aqueous solution was added via syringe. The cloudy solution was stirred for 1 h at room temperature, and then deionized water was added (15 mL/mmol of acid). The remaining milky solution was stirred 30 min at room temperature and then frozen. The frozen solution was then freeze-dried overnight (or longer for large volumes). The sodium salt was usually collected as a white, fluffy light solid directly used for formulation.

2-Acetyl-3,5-di-*iso*-propylphenol (16). To 100.0 g (0.45 mol) of **14** in 500 mL of dry THF at −78 °C was added 965 mL (1.35 mol, 3 equiv) of 1.4 M MeLi. The reaction was stirred overnight while slowly warming to room temperature. EtOAc (500 mL) was slowly added to the reaction mixture, which was subsequently washed (500 mL of 1 N HCl, 500 mL of water, and 500 mL of brine). After drying ($MgSO_4$) and concentration, the residue was purified by SiO_2 chromatography (eluant: 10% EtOAc/hexanes) to afford 72.7 g (0.34 mol, yield: 75%) of **16** as a pale yellow oil that solidified upon standing (mp 36 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): 12.56 (s, 1H), 7.40 (d, J = 2.1 Hz, 1H), 7.30 (d, J = 2.1 Hz, 1H), 3.29 (m, 1H), 2.93 (m, 1H), 1.26 (t, J = 6.7 Hz, 6H), 1.24 (t, J = 6.7 Hz, 6H).

4-Methyl-6,8-di-*iso*-propylcoumarin (18). To 100.0 g (0.45 mol) of **16** suspended in 500 mL of toluene was added 316.0 g (0.91 mol, 2 equiv) of (carbethoxymethylene)triphenylphosphorane. The mixture was heated to reflux and allowed to stir overnight. The mixture was cooled, water was added, and the organics were extracted with 500 mL of EtOAc. The organic layer was washed (water and then brine), dried ($MgSO_4$), concentrated, and purified by SiO_2 chromatography (eluant: 10% EtOAc/hexanes) to give 82.5 g (0.34 mol, yield: 76%) of **18** as a pale yellow oil that solidifies upon standing (mp 54 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33 (d, J = 1.9 Hz, 1H), 7.26 (d, J = 1.9 Hz, 1H), 6.28 (s, 1H), 3.63 (m, 1H), 2.98 (m, 1H), 2.45 (s, 3H), 1.30 (d, J = 5.2 Hz, 6H), 1.29 (d, J = 5.4 Hz, 6H).

(*Z*)-3-(3,5-Di-*iso*-propyl-2-hydroxyphenyl)but-2-ene-1-ol (20). To 1.10 g (4.3 mmol) of **18** in 20 mL of Et_2O at 0 °C was added 0.32 g (5.9 mmol) of sodium aluminum hydride ($NaAlH_4$) portionwise. The reaction was stirred until completion (TLC) while slowly warming to room temperature. The mixture was then cooled to 0 °C and quenched with 0.5 mL of cold water, followed by addition of 1 mL of a 10% aqueous NaOH solution and EtOAc. The precipitate was filtrated over a Celite plug and washed with EtOAc. The organic layer was dried ($MgSO_4$), concentrated, and purified by SiO_2 chromatography (eluant: 20% EtOAc/hexanes) to give 0.96 g (3.9 mmol, yield: 91%) of **20** as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.98 (d, J = 2.0 Hz, 1H), 6.71 (d, J = 2.0 Hz, 1H), 5.95 (td, J = 7.0, 1.2 Hz, 1H), 5.43 (br s, H), 3.94 (d, J = 7.0 Hz, 2H), 3.14 (m, 1H), 2.91 (m, 1H), 2.07 (s, 3H), 1.80 (t, J = 7.0 Hz, 1H), 1.26 (d, J = 7.0 Hz, 6H), 1.22 (d, J = 7.0 Hz, 6H).

(*Z*)-(3,5-Di-*iso*-propyl-2-butoxyphenyl)but-2-ene-1-ol (22g). To a mixture of 700 mg (2.82 mmol) of diol **20** and 620 mg (0.38 mL, 3.38 mmol) of 1-iodobutane in 20 mL of dry DMF was added 2.76 g (8.46 mmol, 1.5 equiv) of Cs_2CO_3 in one time. The mixture was stirred overnight at room temperature, and water (100 mL) was added. The solution was extracted three times with EtOAc (15 mL), and the organic layers were washed twice with water (10 mL) and brine (10 mL) and dried ($MgSO_4$). After removal of the solvents, the crude oil was purified over silica gel column chromatography (eluant: 20% EtOAc/hexanes) to afford 0.77 g (2.54 mmol, yield: 90%) of **22g** as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.01 (d, J = 2.1 Hz, 1H), 6.75 (d, J = 2.1 Hz, 1H), 5.83 (td, J = 7.9, 1.5 Hz, 1H), 3.08 (t, J = 7.6 Hz, 2H), 3.67 (m, 2H), 3.30 (m, 1H), 2.85 (m, 1H), 2.62 (t, J = 5.8 Hz, 1H), 2.11 (s, 3H), 1.71 (m, 2H), 1.42 (m, 2H), 1.23 (d, J = 7.0 Hz, 12H), 0.96 (t, J = 7.3 Hz, 3H).

(*Z*)-2-(3,5-Di-*iso*-propyl-2-butoxyphenyl)but-2-en-1-al (24g). To a mixture of 690 mg (2.27 mmol) of **22g** and 400 mg (3.41 mol, 1.5 equiv) of NMO in 20 mL of dry CH_2Cl_2 was added 80 mg (0.23 mmol, 10%/substrate) of TPAP in one time. The dark solution was stirred at room temperature until completion (TLC analysis) and then filtrated through a silica gel plug. The plug was washed twice with CH_2Cl_2, and the solvents were removed under reduced pressure to afford 0.62 g (2.04 mmol, yield: 90%) of **24g** as a colorless oil directly used in the next step. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.44 (d, J = 8.3 Hz, 1H), 7.11 (d, J = 1.9 Hz, 1H), 6.80 (d, J = 1.9 Hz, 1H), 6.12 (d, J = 8.0 Hz, 1H), 3.64 (t, J = 7.5 Hz, 2H), 3.34 (m, 1H), 2.94 (m, 1H), 2.34 (s, 3H), 1.62 (m, 2H), 1.41 (m, 2H), 1.23 (d, J = 7.2 Hz, 12H), 0.93 (t, J = 7.8 Hz, 3H).

Ethyl (2*E*,4*E*,6*Z*)-7-(3,5-Di-*iso*-propyl-2-butoxybenzene)-3-methylocta-2,4,6-trienoate (26g). To a mixture of 1.27 g (4.79 mmol, 1.2 mL) of triethyl-3-methylphosphonocrotonate diluted in a 15.0/1.5 mL mixture of THF/DMPU was added dropwise 2.3 mL of *n*BuLi (2.5 M in hexane) at −78 °C. After stirring for 30 min at this temperature, 580 mg (1.92 mmol) of the aldehyde **24g** diluted in 5 mL of dry THF was added dropwise. The mixture was then allowed to warm up slowly to room temperature and then quenched with water (50 mL) and extracted twice with EtOAc (15 mL). The organic layer was dried, and after filtration, the solvents were removed under reduced pressure. The crude oil was purified over silica gel column chromatography (eluant: 5% EtOAc/hexanes) to afford 780 mg (1.89 mmol, yield: 98%) of **26g** as an oil (inseparable mixture of isomers). ^{1}H NMR ($CDCl_3$, 500 MHz): δ, 7.02 (d, J = 2.0 Hz, 1H), 6.75 (d, J = 2.0 Hz, 1H), 6.58 (dd, J = 15.0, 11.1 Hz, 1H), 6.24 (d, J = 15.0 Hz, 1H), 6.18 (d, J = 11.1 Hz, 1H), 5.72 (s, 1H), 4.14 (dd, J = 14.4, 7.2 Hz, 2H), 3.64 (m, 2H), 3.32 (m, 1H), 2.83 (m, 1H), 2.21 (s, 3H), 2.14 (s, 3H), 1.61 (m, 2H), 1.41 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H), 1.26 (d, J = 6.6 Hz, 6H), 1.24 (d, J = 6.5 Hz, 6H), 0.91 (t, J = 7.3 Hz, 3H). MS (EI, 70 eV) 413 *m*/*e*: 413 (MH^+, 31), 367 (49), 285 (100), 205 (48).

(2*E*,4*E*,6*Z*)-7-(3,5-Di-*iso*-propyl-2-butoxybenzene)-3-methylocta-2,4,6-trienoic Acid (11g). A mixture of 500 mg (1.21 mmol) of **26g** in 5 mL of THF, 5 mL of MeOH, and 2.5 mL of an aqueous 2 N LiOH solution was refluxed until completion (TLC analysis). After cooling to room temperature, the solvents were removed under reduced pressure, and 10

mL of a 2 N aqueous HCl solution was added. The solution was stirred at room temperature for 10 min and extracted twice with EtOAc (5 mL), and the organic layers were dried over $MgSO_4$. After filtration, the solvents were removed, and the crude pasty oil was recrystallized from CH_3CN to afford 350 mg (0.91 mmol, yield: 75%) of pure **11g** as a white crystal (mp 130 and 139 °C) and a single stereoisomer. ^{1}H NMR ($CDCl_3$, 500 MHz): δ, 7.06 (d, J = 2.2 Hz, 1H), 6.72 (d, J = 2.2 Hz, 1H), 6.57 (dd, J = 15.0, 11.0 Hz, 1H), 6.24 (d, J = 15 Hz, 1H), 6.18 (d, J = 11 Hz, 1H), 5.73 (s, 1H), 3.62 (m, 2H), 3.37 (m, 1H), 2.85 (m, 1H), 2.20 (s, 3H), 2.13 (s, 3H), 1.62 (m, 2H), 1.44 (m, 2H), 1.27 (d, J = 6.6 Hz, 6H), 1.24 (d, J = 6.5 Hz, 6H), 0.91 (t, J = 6.3 Hz, 3H). Anal. ($C_{25}H_{36}O_3$·(1/4)H_2O) C, H. MS (EI, 70 eV) 385 *m/e*: 385 (MH^+, 48), 285 (100), 243 (53), 205 (67). HRMS for $C_{25}H_{37}O_3$ (MH^+) calcd 385.2743; found 385.2763.

2-Acetyl-3,5-di-*tert*-butyl Phenol (17). 2-Acetyl-3,5-di-*tert*-butyl phenol **17** was synthesized according to the procedure described for the synthesis of **16** by adding 965 mL (1.35 mol) of 1.4 M of MeLi to 110.0 g (0.44 mol) of **15** in 500 mL of dry THF at −78 °C. After workup and chromatography (10% EtOAc/hexanes), 83.0 g (0.33 mol, yield: 75%) of **17** was isolated as a pale yellow oil that crystallized upon standing (mp 45 °C, MeOH). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.65 (s, 1H), 7.56 (m, 2H), 2.65 (s, 3H), 1.42 (s, 9H), 1.32 (s, 9H).

2,4-Di-*tert*-amyl-6-iodophenol (29). To a mixture of 14.1 g (60.0 mmol) of **28** and 1.14 g (6.0 mmol) of *p*-toluenesulfonic acid in 100 mL of dry CH_2Cl_2 was added portionwise 14.0 g (66.0 mmol) of NIS at room temperature. After completion of the reaction (TLC), 50 mL of a 10% aqueous solution $Na_2S_2O_3$ was added, and the mixture was stirred for 10 min at room temperature. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The organic layers were collected and dried over $MgSO_4$. After removal of the solvents under reduced pressure, the crude oil was purified over silica gel chromatography (eluant: 5% EtOAc/hexanes) to afford 18.0 g (50.0 mmol, yield: 83%) of **29** as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (d, J = 2.2 Hz, 1H), 7.13 (d, J = 2.2 Hz, 1H), 5.30 (s, 1H), 1.83 (q, J = 7.5 Hz, 2H), 1.58 (q, J = 7.6 Hz, 2H), 1.34 (s, 6H), 1.23 (s, 6H), 0.67 (t, J = 7.4 Hz, 3H), 0.63 (t, J = 7.5 Hz, 3H).

2-Acetyl-3,5-di-*tert*-amyl Phenol (30). To a mixture of 11.5 g (32.2 mmol) of **29** in 150 mL of dry ether was added 50 mL of *n*-BuLi (1.6 M in hexane) dropwise at −78 °C. A white precipitate occured, and the mixture was slowly allowed to warm up to room temperature. When the TLC showed no traces of the starting material, the solution was cooled to −78 °C, and 9.5 mL (8.9 g, 0.1 mol) of dry *N*,*N*-dimethylacetamide diluted in 50 mL of dry ether was added slowly. The solution was warmed up to room temperature and carefully quenched with cold water. The organic layer was separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with water and brine, then dried over $MgSO_4$. After concentration under reduced pressure, the remaining oil was purified over silica gel column chromatography (eluant: 5% EtOAc/hexanes) to yield 2.9 g (10.5 mmol, yield: 33%) of **30** as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.52 (s, 1H), 7.50 (d, J = 2.4 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 2.64 (s, 3H), 1.90 (q, J = 7.6 Hz, 2H), 1.62 (q, J = 7.4 Hz, 2H), 1.38 (s, 6H), 1.28 (s, 6H), 0.68 (t, J = 7.4 Hz, 3H), 0.62 (t, J = 7.6 Hz, 3H).

4-Methyl-6,8-di-*tert*-butylcoumarin (19). 4-Methyl-6,8-di-*tert*-butylcoumarin **19** was synthesized according to the procedure used for the synthesis of **15** by using 83.0 g (0.34 mol) of **17** and 232.9 g (0.67 mol) of (carbethoxymethylene) triphenylphosphorane. After workup and SiO_2 column chromatography (10% EtOAc/hexanes), 73.4 gm (0.27 mol, yield: 79%) of **19** was isolated as pale yellow needles (MeOH); mp 89 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.59 (d, J = 2.0 Hz, 1H), 7.44 (d, J = 2.0 Hz, 1H), 6.27 (s, 1H), 2.45 (s, 3H), 1.51 (s, 9H), 1.36 (s, 9H).

4-Methyl-6,8-di-*tert*-amylcoumarin (31). 4-Methyl-6,8-di-*tert*-amylcoumarin **31** was synthesized according to the procedure described for the synthesis of **18** using 6.5 g (21.5 mmol) of **30** and 18.5 g (53.0 mmol) of (carbethoxymethylene) triphenylphosphorane. After workup and SiO_2 column chromatography (10% EtOAc/hexanes), 5.1 g (17.0 mmol, yield: 80%) of **31** was isolated as a pale brown solid. Pale brown needles (mp 64 °C, hexanes). ^{1}H NMR ($CDCl_3$): δ 7.46 (d, J = 2.3 Hz, 1H), 7.37 (d, J = 2.3 Hz, 1H), 6.27 (s, 1H), 2.45 (s, 3H), 2.00 (q, J = 7.4 Hz, 2H), 1.67 (q, J = 7.4 Hz, 2H), 1.46 (s, 6H), 1.32 (s, 6H), 0.69 (t, J = 7.4 Hz, 3H), 0.62 (t, J = 7.4 Hz, 3H).

(*Z*)-(3,5-Di-*tert*-butyl-2-hydroxyphenyl)but-2-ene-1-ol (21). 21 was synthesized according to the procedure described for the synthesis of **20** using 9.3 gm (34.2 mmol) of **19** in 120 mL of Et_2O and 34.2 mL (34.2 mmol) of 1.0 M lithium aluminum hydride (LAH). After workup and SiO_2 chromatography (20% EtOAC/hexanes), 9.1 g (33.0 mmol, yield: 96%) of **21** was isolated as a white solid (mp 85 °C, hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26 (d, J = 2.0 Hz, 1H), 6.91 (d, J = 2.0 Hz, 1H), 5.98 (dt, J = 7.0, 2.0 Hz, 1H), 5.02 (s, 1H), 3.94 (m, 2H), 2.14 (d, J = 1 Hz, 3H), 1.30 (s, 9H), 1.41 (s, 9H).

(*Z*)-3-(3,5-Di-*tert*-amyl-2-hydroxyphenyl)but-2-en-1-ol (32). 32 was synthesized from 1.00 g (3.3 mmol) of coumarin **31** in the presence of 0.23 g (4.3 mmol) of $NaAlH_4$ according to the procedure described for the synthesis of **20**, and 0.90 g (2.96 mmol, yield: 89%) of **32** was isolated as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.09 (d, J = 2.0 Hz, 1H), 6.79 (d, J = 2.5 Hz, 1H), 5.97 (td, J = 7.0, 1.5 Hz, 1H), 5.38 (s, 1H), 3.91 (t, J = 7.0 Hz, 2H), 2.07 (s, 3H), 1.57 (q, J = 7.5 Hz, 2H), 1.36 (s, 6H), 1.25 (q, J = 7.4 Hz, 2H), 1.24 (s, 6H), 0.66 (t, J = 8.0 Hz, 3H), 0.64 (t, J = 7.5 Hz, 3H).

(*Z*)-3-(3,5-Di-*iso*-propyl-2-methoxyphenyl)but-2-ene-1-ol (22a). 22a was synthesized from 400 mg (1.61 mmol) of **20** and 274 mg (1.93 mmol) of iodomethane in the presence of 786 mg (2.41 mmol) of Cs_2CO_3 according to the procedure described for the synthesis of **22g**, and 393 mg (1.49 mmol, yield: 93%) of **22a** was isolated as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.01 (d, J = 2.3 Hz, 1H), 6.75 (d, J = 2.3 Hz, 1H), 5.81 (t, J = 7.9 Hz, 1H), 3.90 (t, J = 5.8 Hz, 2H), 3.66 (s, 3H), 3.35 (m, 1H), 2.83 (m, 1H), 2.62 (t, J = 5.8 Hz, 1H), 2.11 (s, 3H), 1.24 (d, J = 6.8 Hz, 12H).

(*Z*)-3-(3,5-Di-*iso*-propyl-2-ethoxyphenyl)but-2-ene-1-ol (22b). 22b was synthesized from 300 mg (1.20 mmol) of **20** and 226 mg (1.45 mmol) of iodoethane in the presence of 590 mg (1.8 mmol) of Cs_2CO_3 according to the procedure described for the synthesis of **22g**, and 320 mg (1.16 mmol, yield: 97%) of **22b** was isolated as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.00 (d, J = 2.4 Hz, 1H), 6.74 (d, J = 2.4 Hz, 1H), 5.82 (t, J = 7.8 Hz, 1H), 3.92 (t, J = 5.8 Hz, 2H), 3.76 (dd, J = 14.6, 7.3 Hz, 2H), 3.31 (m, 1H), 2.81 (m, 1H), 2.61 (t, J = 5.8 Hz, 1H), 2.11 (s, 3H), 1.34 (d, J = 7.3 Hz, 3H), 1.22 (d, J = 6.8 Hz, 12H).

(*Z*)-3-[3,5-Di-*iso*-propyl-2-(2-fluoroethoxy)phenyl]but-2-ene-1-ol (22c). 22c was synthesized from 350 mg (1.40 mmol) of **20** and 196 mg (1.55 mmol) of 1-bromo-2-fluoroethane in the presence of 684 mg (2.10 mmol) of Cs_2CO_3 according to the procedure described for the synthesis of **22g**, and 379 mg (1.3 mmol, yield: 92%) of **22c** was isolated as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.03 (d, J = 2.0 Hz, 1H), 6.76 (d, J = 2.0 Hz, 1H), 5.81 (dt, J = 7.5, 1.0 Hz, 1H), 4.65 (dt, J = 55.1, 4.0 Hz, 2H), 3.95 (m, 2H), 3.88 (d, J = 7.5 Hz, 2H), 3.35 (m, 1H), 2.86 (m, 1H), 2.21 (br s, 1H), 2.11 (s, 3H), 1.24 (d, J = 7.0 Hz, 12H).

(*Z*)-3-[3,5-Di-*iso*-propyl-2-(2,2-difluoroethoxy)phenyl]-but-2-ene-1-ol (22d). 22d was synthesized from 330 mg (1.33 mmol) of **20** and 212 mg (1.46 mmol) of 1-bromo-2,2-fluoroethane in the presence of 650 mg (1.99 mmol) of Cs_2CO_3 according to the procedure described for the synthesis of **22g**, and 386 mg (1.23 mmol, yield: 93%) of **22d** was isolated as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.04 (d, J = 2.1 Hz, 1H), 6.76 (d, J = 2.1 Hz, 1H), 5.96 (td, J = 55.1, 4.0 Hz, 1H), 5.82 (td, J = 7.3, 1.5 Hz, 1H), 4.05 (m, 2H), 3.94 (d, J = 7.3 Hz, 2H), 3.36 (m, 1H), 2.96 (s, 1H), 2.81 (m, 1H), 2.11 (s, 3H), 1.24 (d, J = 7.0 Hz, 6H), 1.23 (d, J = 6.7 Hz, 6H).

(*Z*)-3-(3,5-Di-*iso*-propyl-2-propoxyphenyl)but-2-ene-1-ol (22f). 22f was synthesized from 500 mg (2.01 mmol) of **20**

and 272 mg (0.2 mL, 2.21 mmol) of 1-bromopropane in the presence of 320 mg (3.02 mmol) of Cs_2CO_3 according to the procedure described for the synthesis of **22g**, and 537 mg (1.84 mmol, yield: 92%) of **22f** was isolated as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.00 (d, J = 1.9 Hz, 1H), 6.74 (d, J = 1.9 Hz, 1H), 5.81 (t, J = 8.0 Hz, 1H), 3.80 (t, J = 5.9 Hz, 2H), 3.63 (m, 2H), 3.34 (m, 1H), 2.82 (m, 1H), 2.59 (t, J = 5.9 Hz, 1H), 2.11 (s, 3H), 1.83 (m, 2H), 1.23 (d, J = 6.8 Hz, 12H), 1.00 (d, J = 7.8 Hz, 3H).

(*Z*)-3-(3,5-Di-*tert*-butyl-2-methoxyphenyl)but-2-ene-1-ol (23a). 23a was synthesized from 400 mg (1.45 mmol) of **21** and 0.11 mL (245 mg, 1.73 mmol) of iodomethane in the presence of 1.7 g (5.19 mmol) of Cs_2CO_3 according to the procedure described for the synthesis of **22g**, and 371 mg (1.28 mmol, yield: 88%) of **23a** was isolated as an oil that solidifies upon standing (mp 80 °C, hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.29 (d, J = 1.9 Hz, 1H), 6.95 (d, J = 1.9 Hz, 1H), 5.83 (dt, J = 7.0, 2.0 Hz, 1H), 3.85 (d, J = 7.0 Hz, 2H), 3.62 (s, 3H), 2.08 (br s, 1H), 2.02 (s, 3H), 1.38 (s, 9H), 1.27 (s, 9H).

(*Z*)-3-(3,5-Di-*tert*-butyl-2-ethoxyphenyl)but-2-ene-1-ol (23b). 23b was synthesized from 9.0 g (32.0 mmol) of **21** and 2.8 mL (35.2 mmol) of iodoethane in the presence of 14.6 g (96.0 mmol) of cesium fluoride according to the procedure described for the synthesis of **22g**, and 9.2 g (30.5 mmol, yield: 95%) of **23b** was isolated as an oil that solidifies upon standing (mp 75 °C, hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.26 (d, J = 2.0 Hz, 1H), 6.91 (d, J = 2.0 Hz, 1H), 5.82 (dt, J = 7.0, 2.0 Hz, 1H), 3.81 (m, 4H), 2.16 (d, J = 2.0 Hz, 3H), 1.84 (br s, 1H), 1.41 (s, 9H), 1.36 (t, J = 7.0 Hz, 3H), 1.30 (s, 9H). MS (EI, 70 eV) 327 *m/e*: 327 (MH^+, 5), 287 (100), 231 (70).

(*Z*)-3-[3,5-Di-*tert*-butyl-2-(2,2-difluoroethoxy)phenyl]-but-2-ene-1-ol (23c). 23c was synthesized from 2.0 g (7.23 mmol) of **21** and 1.26 g (8.68 mmol) of 1-bromo-2,2-difluoroethane in the presence of 3.53 g (10.85 mmol) of Cs_2CO_3 according to the procedure described for the synthesis of **22g**, and 2.39 g (7.01 mmol, yield: 97%) of **23c** was isolated as a pasty oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.27 (d, J = 2.5 Hz, 1H), 6.92 (d, J = 2.5 Hz, 1H), 6.06 (td, J = 55.4, 4.2 Hz, 1H), 5.79 (t, J = 7.2 Hz, 1H), 3.95 (m, 2H), 3.90 (m, 2H), 2.14 (s, 3H), 1.68 (t, J = 5.9 Hz, 1H), 1.39 (s, 9H), 1.29 (s, 9H).

(*Z*)-3-(3,5-Di-*tert*-butyl-2-propoxyphenyl)but-2-ene-1-ol (23e). 23e was synthesized from 500 mg (1.81 mmol) of diol **21** and 245 mg (0.18 mL, 1.99 mmol) of 1-bromopropane in the presence of 884 mg (2.72 mmol) of Cs_2CO_3 according to the procedure described for the synthesis of **22g**, and 541 mg (1.7 mmol, yield: 94%) of **23e** was isolated as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22 (d, J = 2.0 Hz, 1H), 6.96 (d, J = 2.0 Hz, 1H), 5.80 (t, J = 6.9, 2.0 Hz, 1H), 3.92 (m, 2H), 3.84 (m, 2H), 2.44 (br s, 1H), 2.18 (s, 3H), 1.79 (m, 2H), 1.39 (s, 9H), 1.24 (s, 9H), 0.99 (t, J = 7.0 Hz, 3H).

(*Z*)-[(3,5-Di-*iso*-propyl-2-(2,2,2-trifluoroethoxyphenyl)]-but-2-ene-1-ol (22e). To a mixture of 734 mg (2.96 mmol) of **20** and 1.45 g (0.82 mL, 8.88 mmol) of 2-bromo-1,1,1-trifluoroethane in 20 mL of dry DMF in a 30 mL pressure tube was added 1.93 g (5.92 mmol, 1.5 equiv) of Cs_2CO_3 in one time. The mixture was stirred overnight at 50 °C, and water (50 mL) was added. The solution was extracted three times with EtOAc (10 mL), and the organic layers were washed twice with water (10 mL) and brine (10 mL) and dried ($MgSO_4$). After removal of the solvents, the crude oil was purified over silica gel column chromatography (eluant: 90/10 hexanes/EtOAc) to afford 626 mg (1.90 mmol, yield: 64%) of **22e** as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.02 (d, J = 1.9 Hz, 1H), 6.76 (d, J = 1.9 Hz, 1H), 5.84 (t, J = 7.9 Hz, 1H), 3.85 (d, J = 7.9 Hz, 2H), 3.65 (m, 2H), 3.31 (m, 1H), 2.80 (m, 1H), 2.12 (s, 3H), 1.65 (br m, 1H), 1.23 (d, J = 6.8 Hz, 12H).

(*Z*)-[3,5-Di-*tert*-butyl-2-(2,2,2-trifluoroethoxy)phenyl]-but-2-ene-1-ol (23d). 23d was synthesized from 1.41 g (5.11 mmol) of diol **21** and 2.49 g (1.4 mL, 15.33 mmol) of 1-bromo-2,2,2-trifluoroethane in the presence of 3.33 g (10.22 mmol) of Cs_2CO_3 according to the procedure described for the synthesis of **22e**, and 1.47 g (4.10 mmol, yield: 80%) of **23d** was isolated as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.29 (d, J = 2.7 Hz, 1H), 6.93 (d, J = 2.7 Hz, 1H), 5.80 (t, J = 7.0 Hz, 1H), 4.09 (m, 2H), 4.00 (m, 1H), 3.96 (m, 1H), 2.13 (s, 3H), 1.42 (br s, 1H), 1.39 (s, 9H), 1.29 (s, 9H).

(*Z*)-(3,5-Di-*tert*-amyl-2-methoxyphenyl)but-2-ene-1-ol (33a). 33a was synthesized from 0.66 g (2.17 mmol) of **32** and 0.35 g (0.15 mL, 2.38 mmol) of iodomethane in the presence of 1.00 g (3.26 mmol, 1.5 eq.) of Cs_2CO_3 according to the procedure described for the synthesis of **22g**, and 0.66 g (2.01 mmol, yield: 95%) of **33a** was isolated as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.01 (d, J = 2.5 Hz, 1H), 6.84 (d, J = 2.5 Hz, 1H), 5.83 (td, J = 7.5, 1.0 Hz, 1H), 3.77 (t, J = 7.9 Hz, 2H), 3.65 (s, 3H), 2.59 (t, J = 6.4 Hz, 1H), 2.16 (s, 3H), 1.82 (m, 1H), 1.76 (m, 1H), 1.61 (m, 2H), 1.57 (s, 6H), 1.35 (s, 6H), 0.66 (t, J = 8.0 Hz, 3H), 0.65 (t, J = 7.0 Hz, 3H).

(*Z*)-(3,5-Di-*tert*-amyl-2-ethoxyphenyl)but-2-ene-1-ol (33b). 33b was synthesized from 156 mg (0.51 mmol) of **32** and 88 mg (0.045 mL, 0.56 mmol) of iodoethane in the presence of 250 mg (0.75 mmol, 1.5 eq.) of Cs_2CO_3 according to the procedure described for the synthesis of **22g**, and 158 mg (0.47 mmol, yield: 93%) of **33b** was isolated as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.11 (d, J = 2.0 Hz, 1H), 6.83 (d, J = 2.0 Hz, 1H), 5.82 (td, J = 7.5, 1.5 Hz, 1H), 3.95 (m, 1H), 3.89 (m, 2H), 3.65 (m, 1H), 2.76 (br t, J = 6.1 Hz, 1H), 2.5 (s, 3H), 1.90 (m, 1H), 1.80 (m, 1H), 1.74 (m, 1H), 1.59 (m, 1H), 1.36 (s, 6H), 1.34 (t, J = 7.0 Hz, 3H), 1.25 (s, 6H), 0.65 (t, J = 7.5 Hz, 3H), 0.64 (t, J = 7.6 Hz, 3H).

(*Z*)-[3,5-Di-*tert*-amyl-2-(2,2-difluoroethoxy)phenyl]but-2-ene-1-ol (33c). 33c was synthesized from 400 mg (1.31 mmol) of diol **32** and 209 mg (0.12 mL, 1.44 mmol) of 1-bromo-2,2-difluoroethane in the presence of 640 mg (1.96 mmol, 1.5 equiv) of Cs_2CO_3 according to the procedure described for the synthesis of **22g**, and 434 mg (1.18 mmol, yield: 90%) of **33c** was isolated as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.14 (d, J = 2.4 Hz, 1H), 6.86 (d, J = 2.4 Hz, 1H), 6.04 (tt, J = 55.4, 4.0 Hz, 1H), 5.81 (t, J = 7.5 Hz, 1H), 3.90 (m, 2H), 3.85 (d, J = 7.5 Hz, 2H), 2.14 (s, 3H), 1.82 (m, 1H), 1.75 (m, 2H), 1.65 (br m, 1H), 1.59 (q, J = 7.3 Hz, 2H), 1.36 (s, 6H), 1.26 (s, 6H), 0.67 (t, J = 7.3 Hz, 3H), 0.66 (t, J = 7.3 Hz, 3H).

(*Z*)-(3,5-Di-*tert*-amyl-2-propoxyphenyl)but-2-ene-1-ol (33d). 33d was synthesized from 350 mg (1.15 mmol) of **32** and 155 mg (0.11 mL, 1.26 mmol) of 1-bromopropane in the presence of 562 mg (1.73 mmol, 1.5 equiv) of Cs_2CO_3 according to the procedure described for the synthesis of **22g**, and 380 mg (1.10 mmol, yield: 96%) of **33d** was isolated as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.11 (d, J = 2.4 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 5.81 (t, J = 7.6 Hz, 1H), 3.78 (d, J = 7.6 Hz, 2H), 3.77 (m, 1H), 3.61 (m, 1H), 2.45 (br m, 1H), 2.15 (s, 3H), 1.82 (m, 1H), 1.78 (q, J = 7.0 Hz, 2H), 1.72 (m, 1H), 1.58 (q, J = 7.6 Hz, 2H), 1.36 (s, 6H), 1.25 (s, 6H), 0.98 (t, J = 7.6 Hz, 3H), 0.66 (t, J = 7.6 Hz, 3H), 0.65 (t, J = 7.6 Hz, 3H).

(*Z*)-3-(3,5-Di-*iso*-propyl-2-methoxyphenyl)but-2-en-1-al (24a). 24a was synthesized from 200 mg (0.76 mmol) of **22a** in the presence of 25 mg (0.07 mmol) of TPAP and 133 mg (1.14 mmol) of NMO according to the representative procedure of the synthesis of **24g**, and 186 mg (0.71 mmol, yield: 94%) of **24a** was isolated as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.44 (d, J = 8.3 Hz, 1H), 7.11 (d, J = 2.4 Hz, 1H), 6.80 (d, J = 2.49 Hz, 1H), 6.17 (d, J = 8.0 Hz, 1H), 3.62 (s, 3H), 3.36 (m, 1H), 2.83 (m, 1H), 2.34 (s, 3H), 1.23 (d, J = 6.8 Hz, 12H).

(*Z*)-3-(3,5-Di-*iso*-propyl-2-ethoxyphenyl)but-2-en-1-al (24b). 24b was synthesized from 220 mg (0.79 mmol) of **22b** in the presence of 28 mg (0.08 mmol) of TPAP and 139 mg (1.19 mmol) of NMO according to the representative procedure of the synthesis of **24g**, and 199 mg (0.73 mmol, yield: 92%) of **24b** was isolated as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.44 (d, J = 8.3 Hz, 1H), 7.11 (d, J = 1.9 Hz, 1H), 6.81 (d, J = 1.9 Hz, 1H), 6.11 (d, J = 8.0 Hz, 1H), 3.71 (dd, J = 13.7, 6.8 Hz, 2H), 3.36 (m, 1H), 2.86 (m, 1H), 2.34 (s, 3H), 1.29 (t, J = 6.8 Hz, 3H), 1.24 (d, J = 7.1 Hz, 12H).

(*Z*)-3-[3,5-Di-*iso*-propyl-2-(2-fluoroethoxy)phenyl]but-2-en-1-al (24c). 24c was synthesized from 150 mg (0.60 mmol) of **22c** in the presence of 21 mg (0.06 mmol) of TPAP and 105 mg (0.90 mmol) of NMO according to the representative procedure of the synthesis of **24g**, and 163 mg (0.56 mmol, yield: 93%) of **24c** was isolated as a clear oil. ^{1}H NMR ($CDCl_3$,

400 MHz): δ 9.46 (d, J = 8.2 Hz, 1H), 7.14 (d, J = 2.1 Hz, 1H), 6.82 (d, J = 2.1 Hz, 1H), 6.13 (d, J = 7.9 Hz, 1H), 4.62 (dt, J = 55.1, 4.0 Hz, 2H), 3.97 (m, 1H), 3.94 (m, 1H), 3.39 (m, 1H), 2.92 (m, 1H), 2.34 (s, 3H), 1.24 (d, J = 7.0 Hz, 12H).

(*Z*)-3-[3,5-Di-*iso*-propyl-2-(2,2-difluoroethoxy)phenyl]-but-2-en-1-al (24d). 24d was synthesized from 250 mg (0.80 mmol) of **22d** in the presence of 28 mg (0.08 mmol) of TPAP and 140 mg (1.20 mmol) of NMO according to the representative procedure of the synthesis of **24g**, and 223 mg (0.72 mmol, yield: 90%) of **24d** was isolated as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.43 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 2.0 Hz, 1H), 6.83 (d, J = 2.0 Hz, 1H), 6.15 (dd, J = 8.0, 1.0 Hz, 1H), 5.96 (tt, J = 55.0, 4.0 Hz, 1H), 3.88 (td, J = 13.5, 4.0 Hz, 2H), 3.32 (m, 1H), 2.88 (m, 1H), 2.34 (d, J = 1.0 Hz, 3H), 1.24 (d, J = 7.0 Hz, 6H), 1.23 (d, J = 7.0 Hz, 6H).

(*Z*)-3-[3,5-Di-*iso*-propyl-2-(2,2,2-trifluoroethoxy)phenyl]-but-2-en-1-al (24e). 24e was synthesized from 600 mg (2.42 mmol) of **22e** in the presence of 84 mg (0.24 mmol) of TPAP and 424 mg (3.64 mmol) of NMO according to the representative procedure of the synthesis of **24g**, and 698 mg (2.12 mmol, yield: 88%) of **24e** was isolated as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.46 (d, J = 8.2 Hz, 1H), 7.15 (d, J = 2.1 Hz, 1H), 6.84 (d, J = 2.1 Hz, 1H), 6.18 (dd, J = 8.2, 1.5 Hz, 1H), 4.03 (dd, J = 16.4, 8.2 Hz, 2H), 3.33 (m, 1H), 2.82 (m, 1H), 2.34 (d, J = 1.5 Hz, 3H), 1.24 (d, J = 7.0 Hz, 12H).

(*Z*)-3-(3,5-Di-*iso*-propyl-2-propoxyphenyl)but-2-en-1-al (24f). 24f was synthesized from 500 mg (1.72 mmol) of **22f** in the presence of 59 mg (0.17 mmol) of TPAP and 302 mg (2.58 mmol) of NMO according to the representative procedure of the synthesis of **24g**, and 466 mg (1.61 mmol, yield: 94%) of **24f** was isolated as a clear oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.44 (d, J = 8.3 Hz, 1H), 7.11 (d, J = 1.9 Hz, 1H), 6.80 (d, J = 1.9 Hz, 1H), 6.10 (d, J = 8.0 Hz, 1H), 3.61 (t, J = 6.3 Hz, 2H), 3.37 (m, 1H), 2.82 (m, 1H), 2.33 (s, 3H), 1.63 (m, 2H), 1.24 (t, J = 7.3 Hz, 6H), 1.23 (d, J = 7.3 Hz, 6H), 0.97 (t, J = 7.3 Hz, 3H).

(*Z*)-3-(3,5-Di-*tert*-butyl-2-methoxyphenyl)but-2-en-1-al (25a). 25a was synthesized from 210 mg (0.72 mmol) of **23a** in the presence of 25 mg (0.07 mmol) of TPAP and 127 mg (1.08 mmol) of NMO according to the representative procedure of the synthesis of **24g**, and 180 mg (0.62 mmol, yield: 86%) of **25a** was isolated a pasty oil directly used in the next step. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.48 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 1.9 Hz, 1H), 6.95 (d, J = 1.9 Hz, 1 H), 6.09 (d, J = 8.4 Hz, 1H), 3.66 (s, 3H), 2.33 (s, 3H), 1.40 (s, 9H), 1.34 (s, 9H).

(*Z*)-3-(3,5-Di-*tert*-butyl-2-ethoxyphenyl)but-2-en-1-al (25b). 25b was synthesized from 10.3 g (33.90 mmol) of **23b** in the presence of 600 mg (1.69 mmol) of TPAP and 5.95 g (50.82 mmol) of NMO according to the representative procedure of the synthesis of **24g**, and 8.49 g (28.11 mmol, yield: 83%) of **25b** was isolated as a pasty solid directly used in the next step. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.47 (d, J = 8.5 Hz, 1H), 7.37 (d, J = 2.0 Hz, 1H), 6.96 (d, J = 2.0 Hz, 1 H), 6.10 (d, J = 8.5 Hz, 1H), 3.87 (t, J = 6.3 Hz, 1H), 3.73 (t, J = 6.3 Hz, 1H), 2.36 (s, 3H), 1.41 (s, 9H), 1.31(t, J = 6.3 Hz, 3H), 1.30 (s, 9H).

(*Z*)-3-[3,5-Di-*tert*-butyl-2-(2,2-difluoroethoxy)phenyl]-but-2-en-1-al (25c). 25c was synthesized from 2.20 g (6.46 mmol) of **23c** in the presence of 227 mg (0.65 mmol) of TPAP and 1.13 g (9.69 mmol) of NMO according to the representative procedure of the synthesis of **24g**, and 2.08 g (6.14 mmol, yield: 95%) of **25c** was isolated as a pasty solid directly used in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.47 (d, J = 8.1 Hz, 1H), 7.39 (d, J = 2.4 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1 H), 6.15 (d, J = 8.0 Hz, 1H), 5.87 (td, J = 55.0, 4.0 Hz, 1H), 4.05 (m, 1H), 3.91 (m, 1H), 2.36 (s, 3H), 1.41 (s, 9H), 1.30 (s, 9H).

(*Z*)-3-[3,5-Di-*tert*-butyl-2-(2,2,2-trifluoroethoxy)phenyl]-but-2-en-1-al (25d). 25d was synthesized from 1.4 g (3.9 mmol) of **23d** in the presence of 137 mg (0.39 mmol) of TPAP and 685 mg (5.85 mmol) of NMO according to the representative procedure of the synthesis of **24g**, and 1.31 g (3.67 mmol, yield: 94%) of **25d** was isolated as a pasty solid directly used in the next step. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.50 (d, J = 8.2 Hz, 1H), 7.40 (d, J = 2.7 Hz, 1H), 6.98 (d, J = 2.7 Hz, 1 H), 6.17 (d, J = 8.2 Hz, 1H), 4.10 (m, 1H), 4.02 (m, 1H), 2.36 (s, 3H), 1.41 (s, 9H), 1.30 (s, 9H).

(*Z*)-3-(3,5-Di-*tert*-butyl-2-propoxyphenyl)but-2-en-1-al (25e). 25e was synthesized from 250 mg (0.78 mmol) of **23e** in the presence of 28 mg (0.08 mmol) of TPAP and 137 mg (1.17 mmol) of NMO according to the representative procedure of the synthesis of **24g**, and 234 mg (0.74 mmol, yield: 95%) of **25e** was isolated as a clear pasty oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.43 (d, J = 8.5 Hz, 1H), 7.38 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 2.0 Hz, 1 H), 6.07 (d, J = 8.5 Hz, 1H), 3.89 (m, 1H), 3.81 (m, 1H), 2.34 (s, 3H), 1.72 (m, 2H), 1.40 (s, 9H), 1.27 (s, 9H), 0.98 (t, J = 6.5 Hz, 3H).

(*Z*)-(3,5-Di-*tert*-amyl-2-methoxyphenyl)but-2-en-1-al (34a). 34a was synthesized from 493 mg (1.55 mmol) of **33a** in the presence of 273 mg (2.33 mmol) of NMO and 55.0 mg (0.16 mmol) of TPAP according to the procedure described for the synthesis of **24g**, and 480 mg (1.52 mmol, yield: 98%) of **34a** was isolated as an oil directly used in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.45 (d, J = 8.5 Hz, 1H), 7.21 (d, J = 2.5 Hz, 1H), 6.89 (d, J = 2.5 Hz, 1H), 6.12 (d, J = 8.5 Hz, 1H), 3.61 (s, 3H), 2.35 (s, 3H), 1.90 (m, 2H), 1.59 (m, 2H), 1.36 (s, 6H), 1.26 (s, 6H), 0.67 (t, J = 7.5 Hz, 3H), 0.65 (t, J = 7.5 Hz, 3H).

(*Z*)-(3,5-Di-*tert*-amyl-2-ethoxyphenyl)but-2-en-1-al (34b). 34b was synthesized from 140 mg (0.42 mmol) of **33b** in the presence of 74 mg (0.63 mmol) of NMO and 15 mg (0.04 mmol) of TPAP according to the procedure described for the synthesis of **24g**, and 136 mg (0.41 mmol, yield: 98%) of **34b** was isolated as an oil directly used in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.44 (d, J = 8.2 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 6.08 (dd, J = 8.2, 1.2 Hz, 1H), 3.82 (m, 1H), 3.65 (m, 1H), 2.35 (s, 3H), 1.80 (m, 2H), 1.59 (m, 2H), 1.35 (s, 6H), 1.29 (t, J = 7.0 Hz, 3H), 1.26 (s, 6H), 0.66 (t, J = 7.5 Hz, 3H), 0.65 (t, J = 7.0 Hz, 3H).

(*Z*)-[3,5-Di-*tert*-amyl-2-(2,2-difluoroethoxy)phenyl]but-2-en-1-al (34c). 34c was synthesized from 400 mg (1.09 mmol) of **33c** in the presence of 191 mg (1.63 mmol) of NMO and 35 mg (0.10 mmol) of TPAP according to the procedure described for the synthesis of **24g**, and 363 mg (0.99 mmol, yield: 91%) of **34c** was isolated as an oil directly used in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.45 (d, J = 8.1 Hz, 1H), 7.24 (d, J = 2.4 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 6.05 (dd, J = 8.0, 1.1 Hz, 1H), 5.94 (tt, J = 55.0, 4.0 Hz, 1H), 3.65 (m, 2H), 2.38 (s, 3H), 1.90 (m, 2H), 1.71 (m, 2H), 1.34 (s, 6H), 1.24 (s, 6H), 0.67 (t, J = 7.4 Hz, 3H), 0.66 (t, J = 7.5 Hz, 3H).

(*Z*)-(3,5-Di-*tert*-amyl-2-propoxyphenyl)but-2-en-1-al (34d). 34d was synthesized from 200 mg (0.58 mmol) of **33d** in the presence of 101 mg (0.87 mmol) of NMO and 21 mg (0.06 mmol) of TPAP according to the procedure described for the synthesis of **24g**, and 186 mg (0.53 mmol, yield: 93%) of **34d** was isolated as an oil directly used in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.44 (d, J = 8.2 Hz, 1H), 7.22 (d, J = 2.4 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 6.08 (dd, J = 8.2, 1.2 Hz, 1H), 3.67 (m, 1H), 3.60 (m, 1H), 2.39 (s, 3H), 1.91 (m, 2H), 1.70 (m, 2H), 1.59 (m, 2H), 1.35 (s, 6H), 1.26 (s, 6H), 0.96 (t, J = 7.6 Hz, 3H), 0.67 (t, J = 7.4 Hz, 3H), 0.66 (t, J = 7.5 Hz, 3H).

Ethyl (2*E*,4*E*,6*Z*)-7-(3,5-Di-*iso*-propyl-2-methoxybenzene)-3-methylocta-2,4,6-trienoate (26a). 26a was synthesized from 150 mg (0.58 mmol) of **24a** in the presence of 0.36 mL (380 mg, 1.44 mmol) of triethyl-3-methylphosphonocrotonate and 0.7 mL of *n*-BuLi (2.5 M in hexane) according to the procedure described for the synthesis of **26g**, and 208 mg (0.56 mmol, yield: 97%) of **26a** was isolated as a clear pale yellow oil (mixture of isomers). ^{1}H NMR ($CDCl_3$, 500 MHz): δ, 7.02 (d, J = 2.4 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 6.57 (dd, J = 15.0, 11.0 Hz, 1H), 6.23 (d, J = 11.0 Hz, 1H), 6.20 (d, J = 15.0 Hz, 1H), 5.82 (s, 1H), 4.14 (dd, J = 14.6, 7.3 Hz, 2H), 3.59 (s, 3H), 3.34 (m, 1H), 2.93 (m, 1H), 2.20 (s, 3H), 2.13 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.26 (d, J = 6.3 Hz, 6H), 1.24 (d, J = 6.5 Hz, 6H).

Ethyl (2*E*,4*E*,6*Z*)-7-(3,5-Di-*iso*-propyl-2-ethoxybenzene)-3-methylocta-2,4,6-trienoate (26b). 26b was synthesized from 200 mg (0.73 mmol) of **24b** in the presence of 0.45 mL

(481 mg, 1.82 mmol) of triethyl-3-methylphosphonocrotonate and 0.9 mL of *n*-BuLi (2.5 M in hexane) according to the procedure described for the synthesis of **26g**, and 267 mg (0.69 mmol, yield: 95%) of **26b** was isolated as a clear pale yellow oil (mixture of isomers). ^{1}H NMR ($CDCl_3$, 500 MHz): δ, 7.03 (d, J = 2.4 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 6.59 (dd, J = 15.0, 11.2 Hz, 1H), 6.22 (d, J = 15.0 Hz, 1H), 6.20 (d, J = 11.2 Hz, 1H), 5.74 (s, 1H), 4.15 (dd, J = 14.2, 7.1 Hz, 2H), 3.67 (m, 2H), 3.37 (m, 1H), 2.82 (m, 1H), 2.21 (s, 3H), 2.14 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.23 (d, J = 6.6 Hz, 12H).

Ethyl (2*E*,4*E*,6*Z*)-7-[3,5-Di-*iso*-propyl-2-(2-fluoroethoxy)-benzene]-3-methylocta-2,4,6-trienoate (26c). 26c was synthesized from 150 mg (0.51 mmol) of **24c** in the presence of 0.32 mL (339 mg, 1.28 mmol) of triethyl-3-methylphosphonocrotonate and 0.6 mL of *n*-BuLi (2.5 M in hexane) according to the procedure described for the synthesis of **26g**, and 189 mg (0.47 mmol, yield: 92%) of **26c** was isolated as a clear pale yellow oil (mixture of isomers). ^{1}H NMR ($CDCl_3$, 400 MHz): δ, 7.05 (d, J = 2.5 Hz, 1H), 6.77 (d, J = 2.5 Hz, 1H), 6.56 (dd, J = 15.5, 11.0 Hz, 1H), 6.24 (d, J = 9.5 Hz, 1H), 6.22 (d, J = 15.5 Hz, 1H), 5.75 (s, 1H), 4.60 (dt, J = 55.1, 4.0 Hz, 2H), 4.15 (dd, J = 14.0, 7.0 Hz, 2H), 3.96 (br m, 2H), 3.39 (m, 1H), 2.81 (m, 1H), 2.21 (s, 3H), 2.14 (s, 3H), 1.27 (t, J = 7.0 Hz, 3H), 1.24 (d, J = 7.1 Hz, 6H), 1.22 (d, J = 7.1 Hz, 6H).

Ethyl (2*E*,4*E*,6*Z*)-7-[3,5-Di-*iso*-propyl-2-(2,2-difluoroethoxy)benzene]-3-methylocta-2,4,6-trienoate (26d). 26d was synthesized from 200 mg (0.73 mmol) of **24d** in the presence of 0.45 mL (481 mg, 1.82 mmol) of triethyl-3-methylphosphonocrotonate and 0.9 mL of *n*-BuLi (2.5 M in hexane) according to the procedure described for the synthesis of **26g**, and 276 mg (0.66 mmol, yield: 90%) of **26d** was isolated as a clear pale yellow oil (mixture of isomers). ^{1}H NMR ($CDCl_3$, 400 MHz): δ, 7.06 (d, J = 2.0 Hz, 1H), 6.78 (d, J = 2.0 Hz, 1H), 6.51 (dd, J = 15.5, 11.0 Hz, 1H), 6.27 (d, J = 11.0 Hz, 1H), 6.24 (d, J = 15.5 Hz, 1H), 5.94 (td, J = 55.0, 4.0 Hz, 1H), 5.76 (s, 1H), 4.18 (dd, J = 14.2, 7.1 Hz, 2H), 3.92 (br m, 2H), 3.36 (m, 1H), 2.83 (m, 1H), 2.20 (s, 3H), 2.13 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H), 1.23 (d, J = 7.6 Hz, 6H), 1.21 (d, J = 7.6 Hz, 6H).

Ethyl (2*E*,4*E*,6*Z*)-7-[3,5-Di-*iso*-propyl-2-(2,2,2-trifluorethoxy)benzene)]-3-methylocta-2,4,6-trienoate (26e). 26e was synthesized from 650 mg (1.98 mmol) of **24e** in the presence of 1.22 mL (1.31 g, 4.94 mmol) of triethyl-3-methylphosphonocrotonate and 2.4 mL of *n*-BuLi (2.5 M in hexane) according to the procedure described for the synthesis of **26g**, and 781 mg (1.78 mmol, yield: 90%) of **26e** was isolated as a clear pale yellow oil (mixture of isomers). ^{1}H NMR ($CDCl_3$, 500 MHz): δ, 7.07 (d, J = 2.1 Hz, 1H), 6.78 (d, J = 2.1 Hz, 1H), 6.48 (dd, J = 15.2, 11.0 Hz, 1H), 6.28 (d, J = 11.0 Hz, 1H), 6.26 (d, J = 15.4 Hz, 1H), 5.76 (s, 1H), 4.16 (dd, J = 14.5, 7.2 Hz, 2H), 4.02 (br m, 2H), 3.37 (m, 1H), 2.83 (m, 1H), 2.19 (s, 3H), 2.13 (s, 3H), 1.27 (t, J = 7.3 Hz, 3H), 1.24 (d, J = 7.3 Hz, 6H), 1.23 (d, J = 7.4 Hz, 6H).

Ethyl (2*E*,4*E*,6*Z*)-7-(3,5-Di-*iso*-propyl-2-propoxybenzene)-3-methylocta-2,4,6-trienoate (26f). 26f was synthesized from 400 mg (1.38 mmol) of **24f** in the presence of 0.86 mL (916 mg, 3.46 mmol) of triethyl-3-methylphosphonocrotonate and 1.7 mL of *n*-BuLi (2.5 M in hexane) according to the procedure described for the synthesis of **26g**, and 506 mg (1.26 mmol, yield: 92%) of **26f** was isolated as a clear pale yellow oil (mixture of isomers). ^{1}H NMR ($CDCl_3$, 500 MHz): δ, 7.02 (d, J = 2.4 Hz, 1H), 6.74 (d, J = 2.4 Hz, 1H), 6.58 (dd, J = 15.6, 11.1 Hz, 1H), 6.20 (d, J = 15.6 Hz, 1H), 6.20 (d, J = 11.1 Hz, 1H), 5.73 (s, 1H), 4.13 (dd, J = 14.2, 7.1 Hz, 2H), 3.60 (m, 2H), 3.35 (m, 1H), 2.81 (m, 1H), 2.20 (s, 3H), 2.13 (s, 3H), 1.27 (t, J = 7.3 Hz, 3H), 1.23 (d, J = 6.8 Hz, 12H), 0.96 (t, J = 7.3 Hz, 3H).

Ethyl (2*E*,4*E*,6*Z*)-7-(3,5-Di-*tert*-butyl-2-methoxybenzene)-3-methylocta-2,4,6-trienoate (27a). 27a was synthesized from 180 mg (0.55 mmol) of **25a** according to the procedure described for the synthesis of **26g**, and 207 mg (0.52 mmol, yield: 94%) of **27a** (mixture of isomers) was isolated as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.28 (d, J = 1.9 Hz, 1H), 6.96 (d, J = 1.9 Hz, 1H), 6.61 (dd, J = 15.1, 11.0 Hz, 1H), 6.24 (d, J = 15.1 Hz, 1H), 6.23 (d, J = 11.0 Hz, 1H), 5.78 (s, 1H), 4.18 (dd, J = 15.0,7.2 Hz, 2H), 3.61 (s, 3H), 2.23 (s, 3H), 2.16 (s, 3H), 1.41 (s, 9H), 1.28 (s, 9H), 1.15 (t, J = 7.2 Hz, 3H).

Ethyl (2*E*,4*E*,6*Z*)-7-(3,5-Di-*tert*-butyl-2-ethoxybenzene)-3-methylocta-2,4,6-trienoate (27b). 27b was synthesized from 8.49 g (28.11 mmol) of **25b** according to the procedure described for the synthesis of **26g**, and 10.5 g (24.5 mmol, yield: 87%) of **27b** (mixture of isomers) was isolated as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.29 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 2.0 Hz, 1H), 6.68 (dd, J = 15.2, 11.0 Hz, 1H), 6.26 (d, J = 15.2 Hz, 1H), 6.23 (d, J = 11.0 Hz, 1H), 5.76 (s, 1H), 4.15 (m, 2H), 3.87 (t, J = 6.3 Hz, 1H), 3.69 (t, J = 6.3 Hz, 1H), 2.21 (s, 3H), 2.15 (s, 3H), 1.41 (s, 9H), 1.31 (s, 9H), 1.25 (m, 6H).

Ethyl (2*E*,4*E*,6*Z*)-7-[3,5-Di-*tert*-butyl-2-(2,2-difluoroethoxy)benzene]-3-methylocta-2,4,6-trienoate (27c). 27c was synthesized from 2.00 g (5.91 mmol) of **25c** according to the procedure described for the synthesis of **26g**, and 2.46 g (5.49 mmol, yield: 93%) of **27c** (mixture of isomers) was isolated as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32 (d, J = 2.4 Hz, 1H), 6.96 (d, J = 2.4 Hz, 1H), 6.54 (dd, J = 15.2, 10.9 Hz, 1H), 6.28 (d, J = 15.0 Hz, 1H), 6.24 (d, J = 11.0 Hz, 1H), 5.96 (tt, J = 55.2, 4.1 Hz, 1H), 5.63 (s, 1H), 4.17 (dd, J = 14.2, 7.1 Hz, 2H), 4.04 (m, 1H), 3.86 (m, 1H), 2.22 (s, 3H), 2.14 (s, 3H), 1.42 (s, 9H), 1.31 (s, 9H), 1.28 (t, J = 7.0 Hz, 3H).

Ethyl (2*E*,4*E*,6*Z*)-7-[3,5-Di-*tert*-butyl-2-(2,2,2-trifluoroethoxy)benzene]-3-methylocta-2,4,6-trienoate (27d). 27d was synthesized from 1.25 g (3.51 mmol) of **25d** according to the procedure described for the synthesis of **26g**, and 1.52 g (3.26 mmol, yield: 93%) of **27d** (mixture of isomers) was isolated as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 (d, J = 2.4 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H), 6.55 (dd, J = 15.5, 10.9 Hz, 1H), 6.29 (d, J = 10.9 Hz, 1H), 6.26 (d, J = 15.7 Hz, 1H), 5.77 (s, 1H), 4.21 (m, 1H), 4.15 (dd, J = 14.3, 7.1 Hz, 2H), 4.02 (m, 1H), 2.21 (s, 3H), 2.14 (s, 3H), 1.42 (s, 9H), 1.30 (s, 9H), 1.27 (t, J = 7.3 Hz, 3H).

Ethyl (2*E*,4*E*,6*Z*)-7-(3,5-Di-*tert*-butyl-2-propoxybenzene)-3-methylocta-2,4,6-trienoate (27e). 27e was synthesized from 120 mg (0.38 mmol) of **25e** according to the procedure described for the synthesis of **26g**, and 149 mg (0.35 mmol, yield: 92%) of **27e** (mixture of isomers) was isolated as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26 (d, J = 2.0 Hz, 1H), 6.93 (d, J = 2.0 Hz, 1H), 6.60 (dd, J = 15.0, 11.0 Hz, 1H), 6.21 (d, J = 15.0 Hz, 1H), 6.19 (d, J = 11.0 Hz, 1H), 5.72 (s, 1H), 4.16 (dd, J = 14.9, 7.1 Hz, 2H), 3.78 (m, 1H), 3.61 (m, 1H), 2.21 (s, 3H), 2.17 (s, 3H), 1.68 (m, 2H), 1.40 (s, 9H), 1.14 (s, 9H), 1.12 (t, J = 7.1 Hz, 3H).

Ethyl (2*E*,4*E*,6*Z*)-7-[3,5-Di-*tert*-amyl-2-methoxy)benzene]-3-methylocta-2,4,6-trienoate (35a). 35a was synthesized from 412 mg (1.30 mmol) of **34a** according to the procedure described for the synthesis of **26g**, and 480 mg (1.12 mmol, yield: 87%) of **35a** (mixture of isomers) was isolated as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.13 (d, J = 2.5 Hz, 1H), 6.85 (d, J = 2.5 Hz, 1H), 6.57 (dd, J = 15.0, 11.0 Hz, 1H), 6.24 (d, J = 11.0 Hz, 1H), 6.21 (d, J = 15.0 Hz, 1H), 5.74 (s, 1H), 4.15 (dd, J = 14.6, 7.3 Hz, 2H), 3.58 (s, 3H), 2.21 (s, 3H), 2.12 (s, 3H), 1.92 (m, 2H), 1.58 (m, 2H), 1.37 (s, 6H), 1.27 (t, J = 7.3 Hz, 3H), 1.26 (s, 6H), 0.67 (t, J = 7.5 Hz, 3H), 0.66 (t, J = 7.5 Hz, 3H).

Ethyl (2*E*,4*E*,6*Z*)-7-[3,5-Di-*tert*-amyl-2-ethoxy)benzene]-3-methylocta-2,4,6-trienoate (35b). 35b was synthesized from 125 mg (0.38 mmol) of **34b** according to the procedure described for the synthesis of **26g**, and 186 mg (0.42 mmol, yield: 90%) of **35b** (mixture of isomers) was isolated as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.13 (d, J = 2.4 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 6.60 (dd, J = 15.2, 10.9 Hz, 1H), 6.22 (d, J = 15.3 Hz, 1H), 6.20 (d, J = 11.0 Hz, 1H), 5.73 (s, 1H), 4.15 (dd, J = 14.0, 7.0 Hz, 2H), 3.81 (m, 1H), 3.62 (m, 1H), 2.20 (s, 3H), 2.13 (s, 3H), 1.80 (m, 2H), 1.59 (q, J = 7.4 Hz, 2H), 1.36 (s, 6H), 1.28 (t, J = 7.4 Hz, 3H), 1.25 (s, 6H), 0.66 (t, J = 7.4 Hz, 3H), 0.64 (t, J = 7.4 Hz, 3H).

Ethyl (2*E*,4*E*,6*Z*)-7-[3,5-Di-*tert*-amyl-2-(2,2-difluoroethoxy)benzene]-3-methylocta-2,4,6-trienoate (35c). 35c

was synthesized from 150 mg (0.41 mmol) of **34c** according to the procedure described for the synthesis of **26g**, and 179 mg (0.38 mmol, yield: 92%) of **35c** (mixture of isomers) was isolated as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.17 (d, J = 2.4 Hz, 1H), 6.87 (d, J = 2.4 Hz, 1H), 6.61 (dd, J = 15.4, 10.9 Hz, 1H), 6.26 (d, J = 15.4 Hz, 1H), 6.24 (d, J = 10.9 Hz, 1H), 5.94 (td, J = 55.4, 4.5 Hz, 1H), 5.75 (s, 1H), 4.18 (dd, J = 14.4, 7.3 Hz, 2H), 4.05 (m, 1H), 3.89 (m, 1H), 2.20 (s, 3H), 2.12 (s, 3H), 1.79 (q, J = 7.6 Hz, 2H), 1.59 (q, J = 7.5 Hz, 2H), 1.37 (s, 6H), 1.26 (t, J = 7.3 Hz, 3H), 1.25 (s, 6H), 0.67 (t, J = 7.4 Hz, 3H), 0.65 (t, J = 7.4 Hz, 3H).

Ethyl (2*E*,4*E*,6*Z*)-7-[3,5-Di-*tert*-amyl-2-propoxy)benzene]-3-methylocta-2,4,6-trienoate (35d). 35d was synthesized from 150 mg (0.43 mmol) of **34d** according to the procedure described for the synthesis of **26g**, and 180 mg (0.39 mmol, yield: 91%) of **35d** (mixture of isomers) was isolated as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.13 (d, J = 2.4 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 6.60 (dd, J = 15.2, 10.9 Hz, 1H), 6.22 (d, J = 15.2 Hz, 1H), 6.19 (d, J = 10.9 Hz, 1H), 5.74 (s, 1H), 4.15 (dd, J = 14.3, 7.3 Hz, 2H), 3.72 (m, 1H), 3.59 (m, 1H), 2.24 (s, 3H), 2.13 (s, 3H), 1.81 (m, 2H), 1.70 (m, 2H), 1.60 (q, J = 7.4 Hz, 2H), 1.37 (s, 6H), 1.26 (s, 6H), 0.95 (t, J = 7.6 Hz, 3H), 0.67 (t, J = 7.6 Hz, 3H), 0.66 (t, J = 7.4 Hz, 3H).

(2*E*,4*E*,6*Z*)-7-[3,5-Di-*iso*-propyl-2-methoxybenzene]-3-methylocta-2,4,6-trienoic Acid (11a). Saponification of 200 mg (0.54 mmol) of **26a** according to the procedure described for the synthesis of **11g** affords 111 mg (0.32 mmol, yield: 60%) of **11a** as a white solid (mp 177 and 193 °C, CH_3CN). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.05 (d, J = 2.0 Hz, 1H), 6.76 (d, J = 2.0 Hz, 1H), 6.60 (dd, J = 15.5, 11.0 Hz, 1H), 6.26 (dd, J = 11.0, 1.5 Hz, 1H), 6.24 (d, J = 15.5 Hz, 1H), 5.76 (s, 1H), 3.59 (s, 3H), 3.35 (m, 1H), 2.81 (m, 1H), 2.22 (d, J = 1.5 Hz, 3H), 2.14 (s, 3H), 1.25 (d, J = 7.0 Hz, 6H), 1.23 (d, J = 7.1 Hz, 6H). Anal. ($C_{22}H_{30}O_3$) C, H: calcd, 8.83; found, 8.34. MS (EI, 70 eV) 343 *m/e*: 343 (MH^+, 20), 301 (33), 283 (40), 243 (100). HRMS for $C_{22}H_{31}O_3$ (MH^+): calcd, 343.2273; found, 343.2191.

(2*E*,4*E*,6*Z*)-7-[3,5-Di-*iso*-propyl-2-ethoxybenzene]-3-methylocta-2,4,6-trienoic Acid (11b). Saponification of 235 mg (0.61 mmol) of **26b** according to the procedure described for the synthesis of **11g** affords 137 mg (0.38 mmol, yield: 63%) of **11b** as a white solid (mp 156 °C, CH_3CN). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.04 (d, J = 2.0 Hz, 1H), 6.75 (d, J = 2.0 Hz, 1H,), 6.63 (dd, J = 15.5, 11.0 Hz, 1H), 6.26 (d, J = 15.5 Hz, 1H), 6.23 (d, J = 11.0 Hz, 1H), 5.77 (s, 1H), 3.36 (m, 2H), 3.28 (m, 1H), 2.85 (m, 1H), 2.27 (s, 3H), 2.15 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H), 1.25 (d, J = 6.5 Hz, 6H), 1.23 (d, J = 7.0 Hz, 6H). Anal. ($C_{23}H_{32}O_3 \cdot (1/4)H_2O$) C, H. MS (EI, 70 eV) 357 *m/e*: 357 (MH^+, 18), 297 (38), 257 (100), 205 (55). HRMS for $C_{23}H_{33}O_3$ (MH^+): calcd, 357.2430; found, 357.2408.

(2*E*,4*E*,6*Z*)-7-[3,5-Di-*iso*-propyl-2-(2-fluoroethoxy)benzene]-3-methylocta-2,4,6-trienoic Acid (11c). Saponification of 150 mg (0.37 mmol) of **26c** according to the procedure described for the synthesis of **11g** affords 84 mg (0.22 mmol, yield: 60%) of **11c** as a white solid (mp 162 °C, CH_3CN). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.06 (d, J = 2.0 Hz, 1H), 6.76 (d, J = 2.0 Hz, 1H,), 6.60 (dd, J = 15.5, 11.0 Hz, 1H), 6.28 (d, J = 11.0 Hz, 1H), 6.27 (d, J = 15.5 Hz, 1H), 5.77 (s, 1H), 4.58 (dt, J = 55.1, 4.0 Hz, 2H), 3.91 (m, 2H), 3.40 (m, 1H), 2.85 (m, 1H), 2.22 (s, 3H), 2.15 (s, 3H), 1.24 (d, J = 6.2 Hz, 6H), 1.22 (d, J = 6.3 Hz, 6H). Anal. ($C_{23}H_{31}FO_3$) C, H: calcd, 8.34; found, 8.45. MS (EI, 70 eV) 357 *m/e*: 357 (MH^+, 1), 339 (30), 297 (40), 257 (100), 205 (55). HRMS for $C_{23}H_{32}FO_3$ (MH^+): calcd, 375.2335; found, 375.2316.

(2*E*,4*E*,6*Z*)-7-[3,5-Di-*iso*-propyl-2-(2,2-difluoroethoxy)-benzene]-3-methylocta-2,4,6-trienoic Acid (11d). Saponification of 250 mg (0.59 mmol) of **26d** according to the procedure described for the synthesis of **11g** affords 150 mg (0.38 mmol, yield: 65%) of **11d** as a white solid (mp 141 °C, CH_3CN). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.06 (d, J = 2.0 Hz, 1H), 6.78 (d, J = 2.0 Hz, 1H), 6.56 (dd, J = 15.0, 11.0 Hz, 1H), 6.29 (d, J = 11.0 Hz, 1H), 6.27 (d, J = 15.0 Hz, 1H), 5.94 (tt, J = 55.5, 4.0 Hz, 1H), 5.78 (s, 1H), 3.86 (m, 2H), 3.33 (m, 1H), 2.87 (m, 1H), 2.14 (s, 3H), 2.13 (s, 3H), 1.24 (d, J = 6.3 Hz, 6H), 1.22 (d, J = 6.3 Hz, 6H). Anal. ($C_{23}H_{30}F_2O_3$) C: calcd, 70.39; found, 69.98; H: calcd, 7.70; found, 7.33. MS (EI, 70 eV) 393 *m/e*: 393 (MH^+, 1), 374 (100), 356 (45), 293 (60), 275 (75). HRMS for $C_{23}H_{31}F_2O_3$ (MH^+): calcd, 393.2241; found, 393.2191.

(2*E*,4*E*,6*Z*)-7-[3,5-Di-*iso*-propyl-2-(2,2,2-trifluoroethoxy)benzene]-3-methylocta-2,4,6-trienoic Acid (11e). Saponification of 700 mg (1.59 mmol) of **26e** according to the procedure described for the synthesis of **11g** affords 426 mg (1.04 mmol, yield: 65%) of **11e** as a white solid (mp 148 °C, CH_3CN). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.07 (d, J = 2.1 Hz, 1H), 6.77 (d, J = 2.0 Hz, 1H), 6.55 (dd, J = 15.3, 11.0 Hz, 1H), 6.30 (d, J = 10.3 Hz, 1H), 6.28 (d, J = 15.3 Hz, 1H), 5.78 (s, 1H), 3.99 (m, 2H), 3.35 (m, 1H), 2.87 (m, 1H), 2.21 (s, 3H), 2.14 (s, 3H), 1.25 (d, J = 6.1 Hz, 6H), 1.23 (d, J = 6.9 Hz, 6H). Anal. ($C_{23}H_{29}F_3O_3$) C, H. MS (EI, 70 eV) 411 *m/z*: 411 (MH^+, 40), 393 (62), 311 (100). HRMS for $C_{23}H_{30}F_3O_3$ (MH^+): calcd, 411.2147; found, 411.2160.

(2*E*,4*E*,6*Z*)-7-[3,5-Di-*iso*-propyl-2-propoxybenzene]-3-methylocta-2,4,6-trienoic Acid (11f). Saponification of 455 mg (1.14 mmol) of **26f** according to the procedure described for the synthesis of **11g** affords 262 mg (0.71 mmol, yield: 62%) of **11f** as a white solid (mp 144 °C, CH_3CN). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.04 (d, J = 2.0 Hz, 1H), 6.75 (d, J = 2.0 Hz, 1H,), 6.63 (dd, J = 15.0, 11.0 Hz, 1H), 6.25 (d, J = 15.0 Hz, 1H), 6.23 (d, J = 11.0 Hz, 1H), 5.76 (s, 1H), 3.60 (m, 2H), 3.38 (m, 1H), 2.82 (m, 1H), 2.19 (s, 3H), 2.15 (s, 3H), 1.64 (m, 2H), 1.24 (d, J = 6.5 Hz, 6H), 1.23 (d, J = 6.5 Hz, 6H), 0.97 (t, J = 8.0 Hz, 3H). Anal. ($C_{24}H_{34}O_3 \cdot (1/4)H_2O$) H; C: calcd, 77.80; found, 76.94. MS (EI, 70 eV) 371 *m/e*: 371 (MH^+, 50), 311 (50), 271 (95), 229 (100), 205 (72). HRMS for $C_{24}H_{35}O_3$ (MH^+): calcd, 371.2455; found, 371.2486.

(2*E*,4*E*,6*Z*)-7-(3,5-Di-*tert*-butyl-2-methoxybenzene)-3-methylocta-2,4,6-trienoic Acid (12a). Saponification of 193 mg (0.48 mmol) **27a** according to the procedure described for the synthesis of **11g** affords 113 mg (0.31 mmol, yield: 63%) of **12a** as a white solid (mp 147 and 206 °C, CH_3CN): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29 (d, J = 2.2 Hz, 1H), 6.95 (d, J = 2.0 Hz, 1H), 6.67 (dd, J = 15.0, 11.0 Hz, 1H), 6.26 (d, J = 15.0 Hz, 1H), 6.23 (d, J = 11.0 Hz, 1H), 5.79 (s, 1H), 3.62 (s, 3H), 2.30 (s, 3H), 2.16 (s, 3H), 1.42 (s, 9H), 1.29 (s, 9H). Anal. ($C_{24}H_{34}O_3$) C; H: calcd, 9.25; found, 9.36. MS (EI, 70 eV) 393 *m/e*: 393 (MH^+, 12), 315 (74), 297 (85), 275 (78), 241 (100), 233 (83). HRMS for $C_{24}H_{35}O_3$ (MH^+): calcd, 395.2006; found, 393.2061.

(2*E*,4*E*,6*Z*)-7-(3,5-Di-*tert*-butyl-2-ethoxybenzene)-3-methylocta-2,4,6-trienoic Acid (12b). Saponification of 2.0 g (4.85 mmol) of **27b** according to the procedure described for the synthesis of **11g** affords 949 mg (2.47 mmol, yield: 51%) of **12b** as a white solid (mp 165 and 194 °C, CH_3CN). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.29 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 2.0 Hz, 1H), 6.68 (dd, J = 15.1, 11.0 Hz, 1H), 6.26 (d, J = 15.1 Hz, 1H), 6.23 (dd, J = 11.0, 1.3 Hz, 1H), 5.77 (s, 1H), 3.87 (t, J = 6.3 Hz, 1H), 3.69 (t, J = 6.3 Hz, 1H), 2.24 (s, 3H), 2.16 (d, J = 1.3 Hz, 3H), 1.42 (s, 9H), 1.31 (s, 9H), 1.28 (t, J = 6.3 Hz, 3H). Anal. ($C_{25}H_{36}O_3$) H; C: calcd, 78.08; found, 77.36. MS (EI, 70 eV) 385 *m/e*: 385 (MH^+, 11), 273 (99), 255 (100), 233 (93). HRMS for $C_{25}H_{37}O_3$ (MH^+): calcd, 385.2763; found, 385.2753.

(2*E*,4*E*,6*Z*)-7-(3,5-Di-*tert*-butyl-2-(2,2-difluoroethoxy)-benzene)-3-methylocta-2,4,6-trienoic Acid (12c). Saponification of 2.40 g (5.34 mmol) of **27c** according to the procedure described for the synthesis of **11g** affords 1.37 g (3.26 mmol, yield: 61%) of **12c** as a white solid (mp 165 and 178 °C, CH_3CN). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31 (d, J = 2.4 Hz, 1H), 6.95 (d, J = 2.4 Hz, 1H), 6.59 (dd, J = 15.3, 11.0 Hz, 1H), 6.29 (d, J = 11.0 Hz, 1H), 6.28 (d, J = 15.3 Hz, 1H), 5.96 (dt, J = 55.3 Hz, 4.3 Hz, 1H), 5.78 (s, 1H), 3.95 (m, 2H), 2.22 (s, 3H), 2.15 (s, 3H), 1.41 (s, 9H), 1.30 (s, 9H). Anal. ($C_{25}H_{34}F_2O_3 \cdot (1/4)H_2O$) C, H. MS (EI, 70 eV) 421 *m/z*: 421 (MH^+, 17), 365 (80), 347 (100), 291 (86). HRMS for $C_{25}H_{35}F_2O_3$ (MH^+): calcd, 421.2554; found, 421.2696.

(2*E*,4*E*,6*Z*)-7-[3,5-Di-*tert*-butyl-2-(2,2,2-trifluoroeythoxy)-benzene]-3-methylocta-2,4,6-trienoic Acid (12d). Saponification of 1.4 g (3.00 mmol) of **27d** according to the procedure described for the synthesis of **11g** affords 674 mg (1.65 mmol,

yield: 55%) of **12d** as a white solid (mp 178 °C, CH_3CN). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33 (d, J = 2.4 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H), 6.60 (dd, J = 15.6, 10.7 Hz, 1H), 6.29 (d, J = 10.7 Hz, 1H), 6.27 (d, J = 15.6 Hz, 1H), 5.78 (s, 1H), 4.11 (m, 1H), 4.02 (m, 1H), 2.21 (s, 3H), 2.14 (s, 3H), 1.42 (s, 9H), 1.30 (s, 9H). Anal. ($C_{25}H_{33}F_3O_3$) C; H: calcd, 7.59; found, 7.87. MS (EI, 70 eV) 439 *m/e*: 411 (MH^+, 61), 383 (99), 365 (100) 309 (51). HRMS for $C_{25}H_{34}F_3O_3$ (MH^+): calcd, 439.2460; found, 439.2417.

(2*E*,4*E*,6*Z*)-7-(3,5-Di-*tert*-butyl-2-propoxybenzene)-3-methylocta-2,4,6-trienoic Acid (12e). Saponification of 120 mg (0.28 mmol) of **27e** according to the procedure described for the synthesis of **11g** affords 69 mg (0.17 mmol, yield: 62%) of **12e** as a white solid (mp 155 °C, CH_3CN). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.30 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 2.0 Hz, 1H), 6.67 (dd, J = 15.0, 11.1 Hz, 1H), 6.26 (d, J = 15.0 Hz, 1H), 6.23 (d, J = 11.1 Hz, 1H), 5.75 (s, 1H), 3.89 (m, 1H), 3.69 (m, 1H), 2.27(s, 3H), 2.18 (s, 3H), 1.68 (m, 2H), 1.42 (s, 9H), 1.29 (s, 9H), 0.97 (t, J = 6.3 Hz, 3H). Anal. ($C_{26}H_{38}O_3$) C; H: calcd, 9.61; found: 9.48. MS (EI, 70 eV) 399 *m/z*: 399 (MH^+, 20), 343 (43), 287 (100), 269 (91), 233 (82). HRMS for $C_{26}H_{39}O_3$ (MH^+): calcd, 399.2989; found, 399.3052.

(2*E*,4*E*,6*Z*)-7-(3,5-Di-*tert*-amyl-2-methoxyphenyl)-3-methylocta-2,4,6-trienoic Acid (13a). Saponification of 400 mg (0.28 mmol) of **35a** according to the procedure described for the synthesis of **11g** affords 240 mg (0.18 mmol, yield: 65%) of **13a** as a white solid (mp 140 °C, CH_3CN): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.14 (d, J = 3.0 Hz, 1H), 6.85 (d, J = 3.0 Hz, 1H), 6.62 (dd, J = 15.5, 11.5 Hz, 1H), 6.26 (d, J = 15.5 Hz, 1H), 6.23 (d, J = 11.5 Hz, 1H), 5.76 (s, 1H), 3.58 (s, 3H), 2.23 (s, 3H), 2.13 (s, 3H), 1.90 (m, 2H), 1.59 (q, J = 7.5 Hz, 2H), 1.37 (s, 6H), 1.27 (s, 6H), 0.67 (t, J = 7.5 Hz, 3H), 0.66 (t, J = 7.5 Hz, 3H). Anal. ($C_{26}H_{38}O_3$); C: calcd, 78.35, found, 77.79; H: calcd, 9.01; found, 9.68. MS (EI, 70 eV) 399 *m/z*: 399 (MH^+, 14), 329 (92), 311 (80), 261 (95), 241 (100). HRMS for $C_{26}H_{39}O_3$ (MH^+): calcd, 399.2317; found, 399.2399.

(2*E*,4*E*,6*Z*)-7-(3,5-Di-*tert*-amyl-2-ethoxybenzene)-3-methylocta-2,4,6-trienoic Acid (13b). Saponification of 150 mg (0.34 mmol) of **35b** according to the procedure described for the synthesis of **11g** affords 84 mg (0.20 mmol, yield: 60%) of **13b** as a white solid (mp 138 °C, CH_3CN). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.13 (d, J = 2.1 Hz, 1H), 6.83 (d, J = 2.1 Hz, 1H), 6.65 (dd, J = 15.3, 11.1 Hz, 1H), 6.24 (d, J = 15.3 Hz, 1H), 6.21 (d, J = 11.1 Hz, 1H), 5.75 (s, 1H), 3.82 (m, 1H), 3.64 (m, 1H), 2.21 (s, 3H), 2.14 (s, 3H), 1.81 (m, 2H), 1.58 (q, J = 7.4 Hz, 2H), 1.37 (s, 6H), 1.26 (t, J = 7.3 Hz, 3H), 1.25 (s, 6H), 0.66 (t, J = 7.3 Hz, 3H), 0.65 (t, J = 7.4 Hz, 3H). Anal. ($C_{27}H_{40}O_3$) C; H: calcd, 9.77; found, 9.92. MS (EI, 70 eV) 413 *m/e*: 413 (MH^+, 100), 343 (23), 305 (30), 273 (39). HRMS for $C_{27}H_{41}O_3$ (MH^+): calcd, 413.3056; found, 413.3090.

(2*E*,4*E*,6*Z*)-7-[3,5-Di-*tert*-amyl-2-(2,2-difluoroethoxy)-benzene]-3-methylocta-2,4,6-trienoic Acid (13c). Saponification of 163 mg (0.34 mmol) of **35c** according to the procedure described for the synthesis of **11g** affords 95 mg (0.21 mmol, yield: 62%) of **13c** as a white solid (mp 140 °C, CH_3CN). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.31 (d, J = 2.4 Hz, 1H), 6.95 (d, J = 2.4 Hz, 1H), 6.59 (dd, J = 15.3, 11.0 Hz, 1H), 6.29 (d, J = 11.0 Hz, 1H), 6.28 (d, J = 15.3 Hz, 1H), 5.96 (dt, J = 55.3, 4.3 Hz, 1H), 5.78 (s, 1H), 3.95 (m, 2H), 2.22 (s, 3H), 2.15 (s, 3H), 1.82 (m, 2H), 1.59 (q, J = 7.4 Hz, 2H), 1.33 (s, 6H), 1.25 (s, 6H), 0.67 (t, J = 7.3 Hz, 3H), 0.65 (t, J = 7.4 Hz, 3H). Anal. ($C_{27}H_{38}F_2O_3$) C; H: calcd, 8.54; found, 8.69. MS (EI, 70 eV) 449 *m/e*: 449 (MH^+, 20), 379 (90), 361 (100), 291 (78). HRMS for $C_{27}H_{39}F_2O_3$ (MH^+): calcd, 449.2680; found, 449.2867.

(2*E*,4*E*,6*Z*)-7-(3,5-Di-*tert*-amyl-2-propoxybenzene)-3-methylocta-2,4,6-trienoic Acid (13d). Saponification of 165 mg (0.36 mmol) of **35d** according to the procedure described for the synthesis of **11g** affords 99 mg (0.23 mmol, yield: 64%) of **13d** as a white solid (mp 151 °C, CH_3CN). ^1H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, J = 2.4 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 6.63 (dd, J = 15.2, 11.0 Hz, 1H), 6.23 (d, J = 15.2 Hz, 1H), 6.20 (d, J = 11.0 Hz, 1H), 5.75 (s, 1H), 3.69 (m, 1H), 3.58 (m, 1H), 2.21 (s, 3H), 2.14 (s, 3H), 1.81 (m, 2H), 1.67 (m, 2H), 1.59 (m, 2H), 1.36 (s, 6H), 1.25 (s, 6H), 0.94(t, J = 7.0 Hz, 3H), 0.66 (s, 6H). Anal. ($C_{28}H_{42}O_3$) C; H: calcd, 9.92; found, 10.15. MS (EI, 70 eV) 427 *m/e*: 427 (MH^+, 22), 357 (38), 287 (100), 269 (92), 261 (89). HRMS for $C_{28}H_{43}O_3$ (MH^+): calcd, 427.2628; found, 427.2661.

Biology.

Cotransfection Assay. All cotransfections were carried out in 96-well plates in an automated workstation with CV-1 cells as previously described.

Binding Studies. Receptor binding assays for RARs and RXRs were performed in a similar manner as described in Boehm et al.[9] We used [^{3}H]-9-*cis*-RA as the radioligand for RXRs, and [^{3}H]-ATRA (purchased from NEN-DuPont) for the RARs. K_i values for the analogues were determined by application of the Cheng−Prussof equation.

***db*/*db* Mouse Studies.** *db*/*db* mice were obtained from Jackson Laboratories (Bar Harbor, ME) at 5 weeks of age. Animals were housed in groups of 6 on a 12L:12D light cycle (lights on at 0600 h) with food (Purina 5008) and tap water continuously available. Blood samples were obtained via the tail vein 3 h after dosing on the indicated day. For chronic treatment, mice were gavaged with vehicle and the compound of interest. At the end of the experiments, the animals were weighed and anesthetized. Blood was collected by cardiac puncture prior to euthanization with CO_2. Plasma was used within 1 week for analysis of glucose and triglycerides.

Sprague−Dawley Rat Studies. Seven-week-old male Sprague−Dawley rats (~200 g body weight) were purchased from Harlan Sprague−Dawley (Indianapolis, IN). The animals had free access to Purina 5008 diet (Ralston Purina Co., St. Louis, MO) and tap water, with a 12-h dark, 12-h light cycle (lights on from 06:00 to 18:00). Animals were acclimated in our facility for 5 to 6 days before treatment and were dosed via oral gavage with 1 mL of vehicle each day for 3 days prior to the experiment to acclimate them to the dosing procedure. The vehicle consists of 0.085% povidone (ISP Technologies Inc., New Milford, CT), 1.5% lactose (Quest International, New York, NY), 0.026% Tween-80 (Sigma, St. Louis, MO), and 0.2% v/v antifoam (Dow Corning, Midland, MI). For experiments, the animals were dosed by oral gavage either with the vehicle alone or with a suspension of compounds in the vehicle. Blood was collected from the tail vein of conscious animals, and plasma was prepared and kept frozen at −20 °C until analyzed.

Supporting Information Available: HPLC trace of compounds **11a**−**g**, **12a**−**e**, and **13a**−**d**. This material is available free of charge via the internet at http://pubs.acs.org.

References

(1) Orfanos, C. E.; Ehlert, R.; Gollnick, H. The Retinoids. A Review of Their Clinical Pharmacology and Therapeutic Use. [Review] *Drugs* **1987**, *34*, 459−503.

(2) Peck, G. L.; DiGiovanna, J. J.; Synthetic Retinoids in Dermatology. In *The Retinoids: Biology, Chemistry, and Medicine*, 2nd ed.; Raven Press: New York, 1994; pp 631−658.

(3) Orfanos, C. E.; Zoubouli, C. C.; Almond-Roesler, B.; Geilen, C. C. Current Use and Future Potential Role of Retinoids in Dermatology. [Review] *J. Clin. Oncol.* **1997**, *53*, 358−388.

(4) Boehm, M. F.; Heyman, R. A.; Patel, S.; Stein, R. B.; Nagpal, S. Retinoids: Biological Function and Use in the Treatment of Dermatological Diseases. *Expert Opin. Invest. Drugs* **1995**, *4*, 593−612.

(5) Rosen, J.; Day, A.; Jones, T. K.; Turner Jones, T.; Nadzan, A. M.; Stein, R. B. Intracellular Receptors and Signal Transducers and Activators of Transcription Superfamilies: Novel Targets for Small-Molecule Drug Discovery. *J. Med. Chem.* **1995**, *38*, 4855−4874.

(6) Mangelsdorf, D. J.; Unesono, K.; Evans, R. M.; The Retinoid Receptor. In *The Retinoids: Biology, Chemistry, and Medicine*, 2nd ed.; Raven Press: New York, 1994; pp 319−349.

(7) Heyman, R. A.; Mangelsdorf, D. J.; Dyck, J. A.; Stein, R. B.; Eichele, G.; Evans, R. M.; Thaller, C. 9-Cis Retinoic Acid Is a High Affinity Ligand for the Retinoid Receptor. *Cell* **1992**, *68*, 397−406.

(8) Levin, A. A.; Sturzenbecker, L. J.; Kazmer, S.; Bosakowski, T.; Huselton, C.; Allenby, G.; Speck, J.; Kratzeisen, C.; Rosenberg, M.; Lovey, A.; Grippo, J. F. 9-Cis Retinoic Acid Stereoisomer Binds and Activates the Nuclear Receptor RXRα. *Nature* **1992**, *355*, 359−361.

(9) Boehm, M. F.; Zhang, L.; Badea, B. A.; White, S. K.; Mais, D. E.; Berger, E.; Suto, C. M.; Goldman, M. E.; Heyman, R. A. Synthesis and Structure−Activity Relationships of Novel Retinoid X Receptor-Selective Retinoids. *J. Med. Chem.* **1994**, *37*, 2930−2941.
(10) Sola, X. C.; Kupper, T. A New Rexinoid for Cutaneous T-Cell Lymphoma. *Arch. Dermatol.* **2001**, *137*, 649−652.
(11) Duvic, M.; Hymes, K.; Heald, P.; Breneman, D.; Martin, A. G.; Mykowski, P.; Crowley, C.; Yocum, R. C. Bexarotene Is Effective and Safe for Treatment of Refractory Advanced-Stage Cutaneous T-cells Lymphoma: Multinational Phase II−III Trial Results. *J. Clin. Oncol.* **2001**, *19*, 2456−2471.
(12) Wong, S.-F. Oral Bexarotene in the Treatment of Cutaneous T-cell Lymphoma. *Ann. Pharmacother.* **2001**, *35*, 1056−1065.
(13) Khuri, F. R.; Rigas, J. R.; Figlin, R. A.; Gralla, R. J.; Shin, D. M.; Munden, R.; Fox, N.; Huyghe, M. R.; Kean, Y.; Reich, S. D.; Hong, W. K. Multi-Institutional Phase I/II Trial of Oral Bexarotene in Combination with Cisplatin and Vinorelbine in Previously Untreated Patients with Advanced Nonsmall-Cell Lung Cancer. *J. Clin. Oncol.* **2001**, *19*, 2626−2637.
(14) Boehm, M. F.; Zhang, L.; Zhi, L.; McClurg, R.; Berger, E.; Wagoner, M.; Mais, D. E.; Suto, C. M.; Davies, P. J. A.; Heyman, R. A.; Nazdan A. M. Design and Synthesis of Potent Retinoid X Receptor Selective Ligands That Induce Apoptosis in Leukemia Cells. *J. Med. Chem.* **1995**, *38*, 3146−3155.
(15) Canan Koch, S. S.; Dardashti, L. J.; Cesario, R. M.; Croston, G. E.; Boehm, M. F.; Heyman R. A.; Nazdan A. M. Synthesis of Retinoid X Receptor-Specific Ligands That Are Potent Inducers of Adipogenesis in 3T3-L1 Cells. *J. Med. Chem.* **1999**, *42*, 742−750.
(16) Faul, M. M.; Ratz, A. M.; Sullivan, K. A.; Trankle, W. G.; Winneroski, L. L. Synthesis of Novel Retinoid X Receptor-Selective Retinoids. *J. Org. Chem.* **2001**, *66*, 5772−5782.
(17) Schulman, I. G.; Crombie, D.; Bissonnette, R. P.; Cesario, R.; Roegner, K.; Shao, G.; Heyman, R. A. RXR-Specific Agonists and Modulators: A New Retinoid Pharmacology. In *Handbook of Experimental Pharmacology*; Springer-Verlag: Berlin, 1999; Vol. 139, pp 215−235 and references therein.
(18) Nagpal, S.; Chandraratna, R. A. S. Recent Development in Receptor-Selective Retinoids. *Curr. Pharm. Des.* **2000**, *6*, 919−931 and references therein.
(19) Willson, T. M.; Brown, P. J.; Sternbach, D. D.; Henke, B. R. The PPARs: From Orphan Receptors to Drug Discovery. *J. Med. Chem.* **2000**, *44*, 527−550 and references therein.
(20) Lehnard, J. M. PPARγ/RXR as a Molecular Target for Metabolic Diseases. *Recept. Channels* **2001**, *7*, 249−258.
(21) Jones, A. B. Peroxisome Proliferator-Activated Receptor (PPAR) Modulators: Diabetes and Beyond. *Med. Res. Rev.* **2001**, *21*, 540−552.
(22) Isserman, I.; Green, S. Activation of a Member of the Steroid Hormone Receptor Superfamily by Peroxisome Proliferators. *Nature* **1990**, *347*, 645−650.
(23) Stumvoll, M.; Haring, H. Insulin Resistance and Insulin Sensitizers. *Horm. Res.* **2001**, *55* (Suppl. 2), 3−13.
(24) Mukherkjee, R.; Davies, P. J. A.; Crombie, D. L.; Bischoff, E. D.; Cesario, R. M.; Jow, L.; Hamann, L. G.; Boehm, M. F.; Mondon, C. E.; Nazdan, A. M.; Paterniti, J. R.; Heyman, R. A. Sensitization of Obese Mice to Insulin by Retinoid X Receptor Agonists. *Nature* **1997**, *386*, 407−410.
(25) Vuligonda, V.; Thacher, S. M.; Chandraratna, R. A. S. Enantioselective Syntheses of Potent Retinoid X Receptor Ligands: Differential Biological Activities of Individual Antipodes. *J. Med. Chem.* **2001**, *44*, 2298−2303.
(26) Cesario, R. M.; Klausing, K.; Razzaghi, H.; Crombie, D. L.; Rungta, D.; Heyman, R. A.; Lala, D. The Retinoid LG100754 Is a Novel RXR/PPARγ Agonist and Decreases Glucose Levels In Vivo. *Mol. Endocrinol.* **2001**, *15*, 1360−1369.
(27) Yamauchi, T.; Waki, H.; Kamon, J.; Murakami, K.; Motojima, K.; Komeda, K.; Miki, H.; Kubota, N.; Terauchi, Y.; Tsuchida, A.; Tsuboyama-Kasaoda, N.; Yamauchi, N.; Ide, T.; Hori, W.; Kato, S.; Fukayama, M.; Akanuma, Y.; Ezaki, O.; Itai, A.; Nagai, R.; Kimura, S.; Tobe, K.; Kagechika, H.; Shudo, K.; Kadowaki, T. Inhibition of RXR and PPARγ Ameliorates Diet-Induced Obesity and Type 2 Diabetes. *J. Clin. Invest.* **2001**, *108*, 1001−1013.
(28) Zhang, L.; Nazdan, A. M.; Heyman, R. A.; Love, D. L.; Mais, D. E.; Croston, G. E.; Lamph, W. W.; Boehm, M. F. Discovery of Novel Retinoic Acid Receptor Agonists Having Potent Antiproliferative Activity in Cervical Cells. *J. Med. Chem.* **1996**, *39*, 2659−2663.
(29) Jorgenson, M.; Preparation of Ketones from the Reaction of Organolithium Reagents with Carboxylic Acids. *Org. React.* 1970 **18**, 1−97.
(30) Hamann, L. G.; An Efficient Stereospecific Synthesis of the Dimer-Selective Retinoid X Receptor Modulator (2*E*,4*E*,6*Z*)-7-[5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-(*n*-propoxy)naphthalen-3-yl]-3-methylocta-2,4,6-trienoic Acid. *J. Org. Chem.* **2000**, *65*, 3233−3235.
(31) Nishinaga, A.; Iwasaki, H.; Shimizu, T.; Toyoda, Y.; Matsuura, T. Oxygenation of *tert*-Butylphenols with an Unsaturated Side Chain. *J. Org. Chem.* **1986**, *51*, 2257−2266.
(32) Kallianos, A. G.; Warfield, A. H.; Melvyn, I. S. 3,5-Disubstituted-2-hydroxy Acetophenones. U.S. Patent 3,787,501, 1974.
(33) Wada, A.; Nomoto, Y.; Tano, K.; Yamashita, E.; Ito, M. Synthesis of 9*Z*-9-Substituted Retinoic Acids by Palladium Catalyzed Coupling Reaction of a Vinyl Triflate with Alkenyl Stannanes. *Chem. Pharm. Bull.* **2000**, *49*, 1391−1394.
(34) Pazos, Y.; De Lera, A. Stereoselective Synthesis of 9-*cis*-Retinoic Acid by Suzuki Reaction. *Tetrahedron. Lett.* **1999**, *40*, 8287−8290.
(35) Wada, A.; Hiraishi, S.; Ito, M. Stereoselective Synthesis of 7*E*,9*E*- and 7*E*,9*E*-β-Ionyldeneacetaldehydes by Use of Tricarbonyl Iron Complex. *Chem. Pharm. Bull.* **1994**, *42*, 757−760.
(36) Jansen, F. J. H. M.; Lugtenburg, J. Synthesis and Characterization of all-*E*-(4,4′-13C2)-Astaxanthin. Strategies for Labelling the C15-End Groups of Carotenoids. *Eur. J. Org. Chem.* **2000**, *5*, 829−836.
(37) Dominguez, B.; Pazos, Y.; De Lera, A. R. Stereocontrolled Synthesis of 6-*s*-*cis*- and 6-*s*-*trans*-Locked 9*Z*-Retinoids by Hydroxyl-Accelerated Stille Coupling of (*Z*)-tri-*n*-Butylstannylbut-2-en-1-ol and Bicyclic Dienyl Triflates. *J. Org. Chem.* **2000**, *65*, 5917−5925.
(38) For a review of dianion chemistry, see: Thompson, C. M. *Dianion Chemistry in Organic Synthesis*; CRC Press: Boca Raton, FL, 1994.
(39) Liu, S.; Ogilvie, K. M.; Klausing, K.; Lawson, M. A.; Jolley, D.; Danmei, L.; Bilakovics, J.; Pascual, B.; Hein, N.; Urcan, M.; Leibowitz, M. D. Mechanism of Selective Retinoid X Receptor Agonist-Induced Hypothyroidism in the Rat. *Endocrinology*, in press.
(40) Schultz, Tu, H., Jr.; Luk, A.; Repa, J. J.; Medina, J. C.; Li, L.; Schwendner, S.; Wang, S.; Thoolen, M.; Mangelsdorf, D. J.; Lustig, K. D.; Shan, B. Role of LXRs in Control of Lipogenesis. *Genes Dev.* **2000**, *14* , 2831−2838.
(41) Cannan Koch, S. S.; Dardashti, L. J.; Hebert, J. J.; White, S. K.; Croston, G. E.; Flatten, K. S.; Heyman, R. A.; Nazdan, A. M. Identification of the First Retinoic X Receptor Homodimer Antagonist. *J. Med. Chem.* **1996**, *39*, 3229−3234.
(42) Lala, D. S.; Mukherjee, R.; Schulman, I. G.; Cannan Koch, S. S.; Dardashti, L. J.; Nazdan, A. M.; Croston, G. E.; Evans, R. M.; Heyman, R. A. Activation of Specific Heterodimers by an Antagonist of RXR Homodimers. *Nature* **1996**, *383*, 450−453.
(43) This unusual effect is know as the phantom ligand effect. See: Schulman, I. G.; Chuan, L.; Scwabe, J. W. R.; Evans, R. M. The Phantom Ligand Effect: Allosteric Control of Transcription by the Retinoid X Receptor. *Genes & Dev.* **1997**, *11*, 299−308.
(44) Standeven, A. M.; Thacher, S. M.; Yuan, Y.-D.; Escobar, M.; Vuligonda, V.; Beard, R. L.; Chadraratna, A. S. Retinoid X Receptor Agonist Elevation of Serum Triglycerides in Rats by Potentiation of Retinoic Acid Receptor Agonist Induction or by Action as Single Agents. *Biochem. Pharmacol.* **2001**, *62*, 1501−1509.
(45) Weatherman, R. V.; Fletterick, R. J.; Scanlan, T. S. Nuclear-Receptor Ligands and Ligand-Binding Domains. *Annu. Rev. Biochem.* **1999**, *68*, 559−581.

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