Design, Synthesis, and Structure−Activity Relationship Studies of Novel 6,7-Locked-[7-(2-alkoxy-3,5-dialkylbenzene)-3-methylocta]-2,4,6-trienoic Acids

Pierre-Yves Michellys,*[,§,+] Robert J. Ardecky,[§] Jyun-Hung Chen,[§] Jennifer D'Arrigo,[#] Timothy A. Grese,[⊗] Donald S. Karanewsky,[§,+] Mark D. Leibowitz,[||] Sha Liu,[||] Dale A. Mais,[#] Christopher M. Mapes,[×] Chahrzad Montrose-Rafizadeh,[£] Katheen M. Ogilvie[⊗,†] Anne Reifel-Miller,[▽] Deepa Rungta,[#] Anthony W. Thompson,[§,‡] John S. Tyhonas,[§] and Marcus F. Boehm[⊥,§]

Departments of Medicinal Chemistry, Pharmacology, and New Leads Discovery, Ligand Pharmaceuticals, Inc., 10275 Science Center Drive, San Diego, California 92121, and Division of Endocrine Research, Discovery Chemistry Research, and Lead Optimization Biology, Eli Lilly Research Laboratories, Indianapolis, Indiana

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Retinoid X receptor:peroxisome proliferative-activated receptor (RXR:PPAR) heterodimers play a critical role in the regulation of glucose (RXR/PPARγ) and lipid metabolism (RXR/PPARα). Previously, we described a concise structure−activity relationship study of selective RXR modulators possessing a (*2E*,*4E*,*6Z*)-3-methyl-7-(3,5-dialkyl-6-alkoxyphenyl)-octa-2,4,6-trienoic acid scaffold. These studies were focused on the 2-position alkoxy side chain. We describe here the design and synthesis of a novel series of RXR selective modulators possessing the same aromatic core structure with the addition of a ring locked 6−7-*Z*-olefin on the trienoic acid moiety. The synthesis and structure−activity relationship studies of these 6,7-locked cyclopentenyl, phenyl, thienyl, furan, and pyridine-trienoic acid derivatives is presented herein.

Introduction

Retinoids play a major role in a wide variety of biological functions, such as cell differentiation, proliferation, and embryonic development in vertebrates.[1] Retinoids, such as all-*trans*-retinoic acid (ATRA), 13-*cis*-retinoic acid (13-*cis*-RA), 9-*cis*-retinoic acid (9-*cis*-RA, Panretin) and more recently **1** (LGD1069, Targretin, Figure 1), are administered for treatment of numerous skin diseases such as psoriasis, acne, Kaposi's sarcoma, and CTCL.[2] In addition, these and other retinoids have been evaluated in both chemotherapy and chemoprevention of various cancers.[3] Retinoids exert their biological activity through retinoid receptors which belong to the superfamily of intracellular nuclear receptors. Activation of these receptors results in regulation of gene transcription.[4] The retinoid receptors are divided into two distinct families of homologous receptors, the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs). Each family is further divided into three receptor subtypes α, β, and γ each encoded by a single gene.[5]

RXR has long been recognized to form homodimers (RXR:RXR) and heterodimers with various other nuclear receptors, including RAR, TR, VDR, NGFIB, LXR, FXR, and PPAR.[5,6] RXR:PPAR heterodimers play a major role in the regulation of both glucose (RXR/PPARγ) and lipid metabolism (RXR/PPARα).[7] Classic RXR agonists such as Targretin and compound **2** (LG100268, Figure 1) are known to be very effective insulin-sensitizing agents,[6,8] but suffer from undesirable side effects such as a suppression of the thyroid hormone axis and an increase of plasma triglycerides.[8b] Recently, we demonstrated that the RXR-selective modulator **4** (LG101506, Figure 1) possesses good hypoglycemic efficacy (*db*/*db* mouse model) and a different side effects profile from the classic RXR agonists (e.g., **2**) in a rat model (Sprague Dawley rats).[9]

RXR-selective molecules representing several structurally different scaffolds are represented in Figure 1.[10] Analogues of the potent RAR compound ALRT1550[11] (compounds **5** and **6**) possess cyclopentyl or cyclopropyl ring replacements of the 6−7-olefin in the trienoic acid moiety.[12,13] This effectively locks the 6,7-olefin in a cis conformation, which instills potent RXR activity. The thioethers **7a**,**b** and more recently the 1,2,3,4-tetrahydroquinoline-6-fluorotrienoic acid derivative **8** have also been described as potent RXR selective ligands.[14,15] Other structures such as the diazepinylbenzoic acid derivative **14** (HX600, a potent RXR agonist),[16] **11** (AGN191701, an RXR selective pan-agonist that is an effective modulator of endothelial cell proliferation),[17] and compound **12** (SR11246, an RXR selective agonist that shows antiproliferative activity on prostate cancer cells)[18] have been described. Compound **9** (AGN 194204) has recently been reported to be a very potent hypoglycemic agent.[19] Interestingly, its antipode does not show any hypoglycemic activity. Heterodimer selectivity of **9** and its antipode is unknown, but one may speculate that one antipode activates the RXR:PPARγ heterodimer while the other does not.

Previous published results have already demonstrated that similar molecules having a cyclopentyl-

* Correspondence author. Current address: Department of Medicinal Chemistry, Genomics Institute of Novartis Research Foundation, San Diego, CA 92121. Phone: (858) 332 4781, Fax: (858) 812 1648. E-mail: pmichellys@gnf.org
[§] Department of Medicinal Chemistry, Ligand Pharmaceuticals.
[||] Department of Pharmacology, Ligand Pharmaceuticals.
[▽] Division of Endocrine Research, Eli Lilly Research Laboratories.
[⊗] Discovery Chemistry Research, Eli Lilly Research Laboratories.
[#] Department of New Leads Discovery, Ligand Pharmaceuticals.
[£] Lead Optimization Biology, Eli Lilly Research Laboratories.
[⊥] Current address: Conforma Therapeutics, San Diego, CA
[+] Current address: Genomics Institute of Novartis Research Foundation, San Diego, CA
[‡] Current address: Roche Bioscience, Palo Alto, CA.
[×] Current address: Johnson and Johnson, San Diego, CA.
[†] Current address: Pfizer Inc., San Diego, CA.

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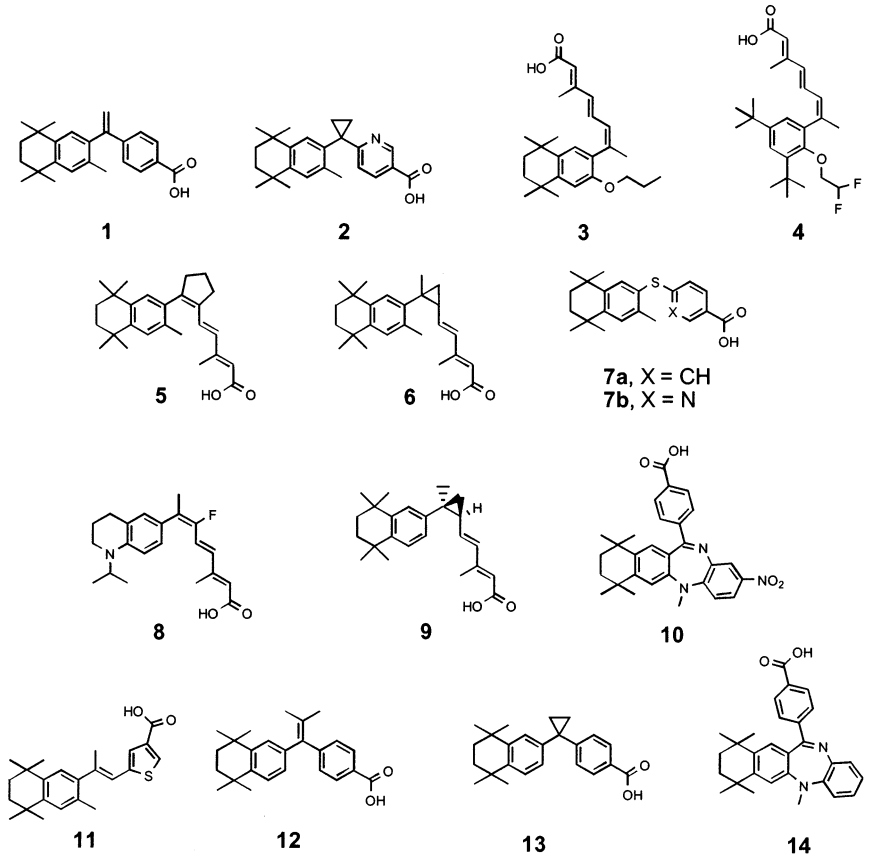


Figure 1. RXR-selective synthetic ligands.

locked or cyclopropyl-locked trienoic acid linked to a substituted 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl moiety possess RXR agonist selectivity (see **5**, **6**, and **9**, Figure 1). More recently, we discovered that the use of a fluorinated alkoxy side chain greatly increases the plasma concentration of compounds such as **4** as compared to its nonfluorinated analogues.[9] In the course of our structure activity relationship studies to design new and potentially more stable RXR modulators, we combined the restricted locked-trienoic acid motif of molecules **5** and **6** with the 3,5-dialkyl-6-fluoroalkoxybenzene platform present in **4**. We describe here a structure−activity relationship study of new RXR-selective modulators possessing various dienoic-acids combined with fluorinated 6-alkoxy side-chains (Figure 2) which results in comparable or improved in vitro profiles over our lead compound **4**.

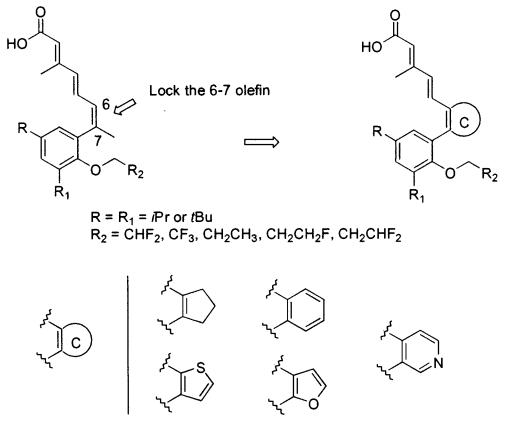
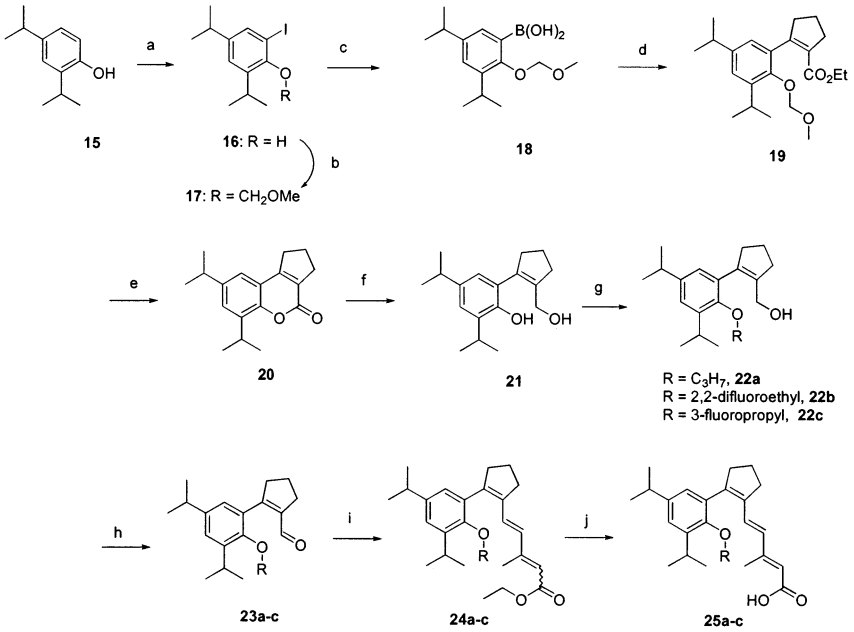


Figure 2.

Chemistry

Ortho-iodination of the 2,4-di-*iso*-propylphenol **15** proceeds in yields greater than 90% by using 1.1 equiv of *N*-iodosuccinimide (NIS) and a catalytic amount (10%) of TsOH in CH_2Cl_2. Introduction of the MOM protecting group onto the free phenol **16** is achieved quantitatively by using chloromethyl methyl ether and NaH in DMF. The boronic acid **18** is obtained by lithiating **17** in a 1:2 mixture of THF/Et_2O with *n*-BuLi (1.2 equiv) at −78 °C, followed by a quench with an excess (2.3 equiv) of $B(OMe)_3$. Once the sample is warmed to RT, the crude boronate is stirred with 1 N HCl, releasing the corresponding boronic acid **18** in good yield (80−90%). The principle synthetic step involved in the preparation of compounds **25a**−**c** is a Suzuki coupling of **18** with the commercially available ethyl-2-(trifluoromethylsulfonyloxy)-1-cyclopentene-1-carboxylate using 10% $Pd(PPh_3)_4$ and 2 equiv of 2 N aq. Na_2CO_3 in refluxing toluene/EtOH (1:1).[20] Submitted to these conditions, the reaction smoothly produced the adduct **19** in excellent yield (>90%). The cyclization of **19** into the coumarin **20** proceeds quantitatively by simple acidic cleavage (6 N HCl, THF, RT) of the MOM group. Reduction of **20** to the phenolic alcohol **21** is achieved using 1 equiv of $NaAlH_4$ in THF at 0 °C. The alkoxy side chain is easily introduced by a selective alkylation of the phenol (Cs_2CO_3 in DMF at room temperature), affording **22a**−**c** in almost quantitative yields. Oxidation of the resultant allylic alcohols **22a**−**c** with a catalytic amount (5−10%) of tetrapropylammonium perruthenate (TPAP) and an excess (1.5 eq.) of 4-methylmorpholine *N*-oxide (NMO) in CH_2Cl_2 yields the corresponding aldehydes **23a**−**c**.[9,21] These aldehydes are directly subjected to a Horner-

Scheme 1 Cyclopentenyl Dienoic Acids Synthetic Path[a]



[a] Reagents and conditions: (a) NIS, TsOH, CH_2Cl_2, RT. (b) NaH, MOMCl, DMF, 0 °C to RT. (c) *n*-BuLi, $B(OMe)_3$, THF/diethyl ether, −78 °C to RT then HCl. (d) Ethyl-2-(trifluoromethylsulfonyloxy)-1-cyclopentene-1-carboxylate, $Pd(PPh_3)_4$, 2 N aq. Na_2CO_3, toluene/ethanol, reflux. (e) Aq. 6 N HCl, THF, RT. (f) $NaAlH_4$, THF, 0 °C to RT. (g) R−Br, Cs_2CO_3, DMF, RT. (h) TPAP, NMO, CH_2Cl_2, RT. (i) Triethyl-3-methylphosphonocrotonate, *n*-BuLi, THF/DMPU, −78 °C to RT. (j) 2 N aq. LiOH, EtOH, reflux then HCl and recrystallization from CH_3CN.

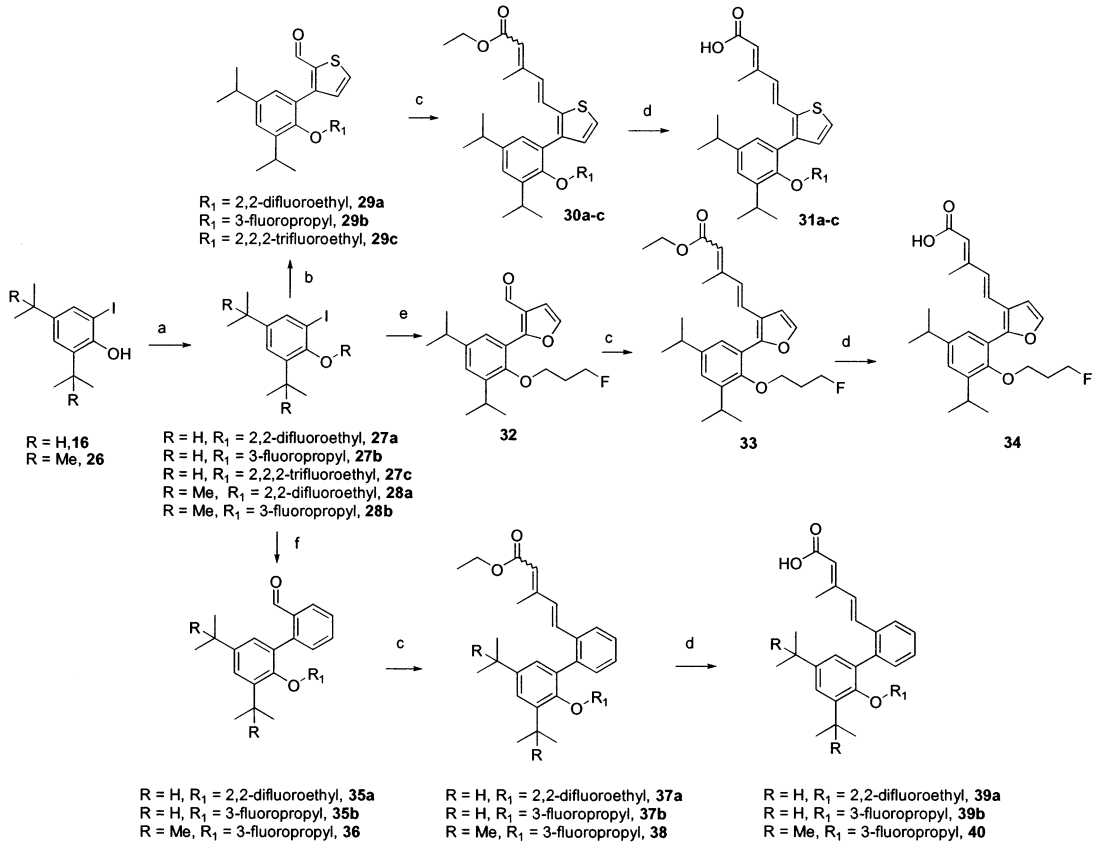
Wadsworth-Emmons reaction with the anion of triethyl-3-methylphosphonocrotonate (previously prepared by slow addition of *n*-BuLi to a solution of the phosphonate in THF-DMPU (1:2) at −78 °C) to afford the corresponding esters **24a**−**c** in a combined yield greater than 85%.[9,10d,22] Hydrolysis of the esters **24a**−**c** with 2 N LiOH in refluxing methanol/THF afford the crude dienoic acids **25a**−**c**. Recrystallization of these crude acids from CH_3CN delivers the pure (2*Z*,4*E*)-dienoic acids in good yield and excellent isomeric purity (>95%).

Schemes 2 and 3 describe the synthesis of selected aromatic and heteroaromatic dienoic acids. The phenols **16** and **26** were easily alkylated with various fluoroalkyl bromides using the reaction condition described in Scheme 1. Due to the high volatility and reduced reactivity of the 2-bromo-1,1,1-trifluoroethane, a variation of this procedure was used to install the 2,2,2-trifluoroethoxy side chains of **27c**. The reaction was conducted in a sealed tube at 50 °C for 16 h using 2 equiv of 2-bromo-1,1,1-trifluoroethane followed by usual workup and column purification. Under these conditions, **27c** was obtained in 65% yield.[9] Every locked structure **29a**−**c**, **32**, **35a**,**b**, **36**, **42**, and **45** was synthesized by using a Suzuki coupling between the iodides **27a**−**c** or **28a**,**b** and the 2-formylfuran, 2-formylthiophene, and 2-formylbenzene boronic acids (Scheme 2) or between **41** and 3-bromo-4-formyl pyridine or ethyl-2-(trifluoromethylsulfonyloxy)-1-cyclopentene-1-carboxylate (Scheme 3). In each case, the reactions were conducted using standard coupling procedure (aq. Na_2CO_3, $Pd(PPh_3)_4$, in refluxing toluene/EtOH) except for the synthesis of **32** where a solution of aqueous Na_2CO_3 and $Pd(PPh_3)_4$ (5−10%) in refluxing DME was used (no desired product **32** was observed using the standard conditions). This reaction was particularly capricious due to the high reactivity of this boronic acid and typically gave very low yields of desired product (<10%). Otherwise **29a**−**c**, **35a**,**b** **36**, **42**, and **45** (Scheme 2) were obtained in very good yield (>90%). The boronic acid **41** (Scheme 3) was synthesized from the iodide **27c** by trapping the corresponding lithiated anion (prepared from slow addition of *n*-BuLi to a solution of **27c** in the presence of TMEDA at −78 °C) with $B(OMe)_3$ followed by acidic workup. **29a**−**c**, **32**, **35a**,**b**, **36**, **42**, and **45** were directly subjected to the reaction sequence described previously in Scheme 1 to produce the crude acids **31a**−**c**, **34**, **39a**,**b**, **40**, **44**, and **49** that were purified by recrystallization from CH_3CN.

Compounds **55a**,**b** (Scheme 4) were synthesized according to the synthetic path described in Scheme 4 from the commercially available 2-*tert*-butyl-4-ethylphenol **50** and represent a beginning for structure−activity relationship studies around the benzene core ring. The acids **55a**,**b** were purified by recrystallization from CH_3CN.

Scheme 5 describes the introduction of the 3,3-difluoropropoxy side-chain. Initial attempts to introduce a 3,3,3-trifluoropropyl side chain using 3-bromo-1,1,1-trifluoropropanewere unsuccessful. No desired product was observed using various bases (NaH, K_2CO_3, CsF, Cs_2CO_3) or solvents (DMF, THF, or DMSO) even with the use of a pressure tube. However, subsequent attempts to synthesize the 1,1-difluoropropoxy side chain from the corresponding 3-hydroxypropoxy compound **56** were successful. Alkylation of the phenol **26** with *tert*-butyldimethysilyloxy-3-bromopropane in DMF in the presence of NaH at 0 °C, followed by cleavage of the TBS group with TBAF, afforded the alcohol **56**. Oxidation of **56** with PCC/Celite in CH_2Cl_2 yielded the corresponding aldehyde **57** directly followed by treatment with DAST in CH_2Cl_2 at room temperature overnight to give the fluorinated intermediate **58**.[23] Compound **58** was isolated in good overall yield (>75%).

Scheme 2. Thienyl, Furyl, and Phenyl Dienoic Acids Synthesis[a]



[a] Reagents and conditions: (a) Cs_2CO_3, R−Br, DMF, RT, except for **27c** (50 °C in a sealed tube, 16 h). (b) $Pd(PPh_3)_4$, 2-formylthiophene-3-boronic acid, Na_2CO_3, toluene/EtOH, reflux. (c) Triethyl-3-methylphosphonocrotonate, *n*-BuLi, THF/DMPU, −78 °C to RT. (d) 2 N aq. LiOH, EtOH, reflux then HCl and recrystallization from CH_3CN. (e) 2-Formylfuran-3-boronic acid, Na_2CO_3, DME, reflux. (f) 2-Formylbenzene boronic acid, Na_2CO_3, toluene/EtOH, reflux.

Synthesis of **61** followed the synthetic path described in Scheme 3 using the iodide **58** and 2-formylthiophene-3-boronic acid. The acid **61** was purified by recrystallization from CH_3CN.

Results

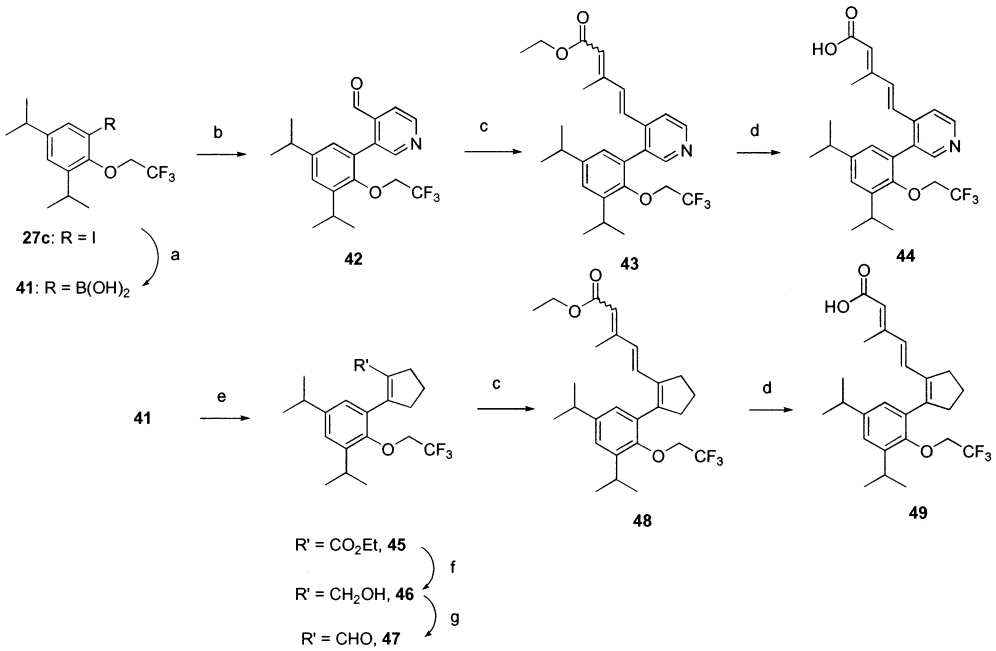
Pharmacological Relevance of RXR-Selective Modulators. The pharmacology of RXR-selective modulators such as compound **4** was fully described in our previous communication.[9] The ability of **4** to lower plasma glucose was evaluated in the *db*/*db* mouse and is summarized in Table 1. These mice have 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 **2** 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. Compound **4** was given orally as a single agent at 30 mg kg^{-1} day^{-1}, while **2** and BRL49653 were used at 10 mg kg^{-1} day^{-1}. After 7 days of treatment, compound **4** was as efficacious as BRL 49653, which typically gives 55% glucose reduction in our hands.

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.[24] Triglycerides and T4 levels were measured at 2 and 24 h, respectively, following administration of a single oral dose (30 mg/kg) to naïve animals. The results are shown in Table 3. At 2 h post dose, the agonist **2** raised triglycerides substantially, while the RXR modulator **4** did not. At 24 h post dose, the agonist **2** caused a significant decrease in T4 levels (2.2-fold) and **4** did not. In summary, compound **4** showed the same efficacy on the glucose endpoint as either BRL49653 or **2** but did not raise triglycerides nor decrease T4 levels in Sprague Dawley rats, overcoming two of the physiological side effects associated with RXR agonists such as **2** in these animal models. As a result, compound **4** is used as our standard for in vitro profiling of the new RXR-selective modulators described in this communication.

Biological Evaluation of Compounds 25a−c, 31a−c, 34, 39a,b, 40, 44, 49, 55a,b, and 61. The binding to RXRα,β,γ, RARα,β,γ, and PPARα,γ of each synthesized compound was characterized by competition with ^{3}[H]-9-*cis*-RA for RXRs and ^{3}[H]-ATRA for RARs (shown as K_i, Table 3). The binding affinity for the PPARs was characterized using a proprietary radioactive ligand as described previously.[25] The RXR transcriptional activation profile of each compound was determined in CV-1 cells with the AOX response element used as the reporter. The efficacy was measured relative to LGD1069 for RXRs and ATRA for RARs (Table 4). For the RXR:PPARγ heterodimer activity, the same AOX reporter construct was used and the efficacy was measured relative to BRL49653 for PPARγ.

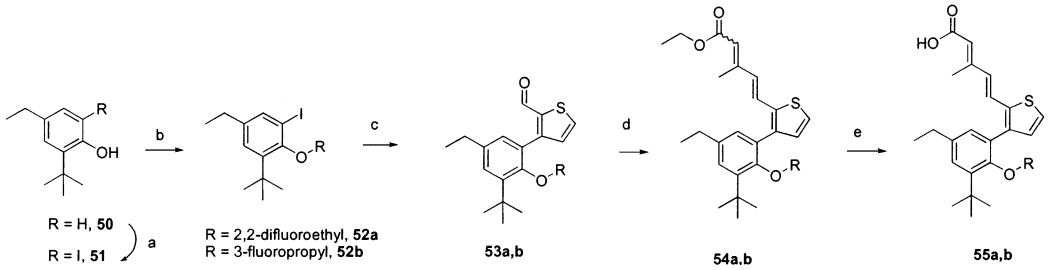
It has been already demonstrated that RXR agonists such as compound **2** (entry 1, Table 4) activate the RXR:

Scheme 3. 3-Pyridyl Dienoic Acid Synthesis[a]



[a] Reagents and conditions: (a) *n*-BuLi, TMEDA, THF, −78 °C then aq. HCl. (b) $Pd(PPh_3)_4$, 3-bromo-4-formylpyridine, Na_2CO_3, toluene/EtOH, reflux. (c) Triethyl-3-methylphosphonocrotonate, *n*-BuLi, THF/DMPU, −78 °C to RT. (d) 2 N aq. LiOH, EtOH, reflux then HCl and recrystallization from CH_3CN. (e) Ethyl-2-(trifluoromethylsulfonyloxy)-1-cyclopentene-1-carboxylate, $Pd(PPh_3)_4$, 2 N aq. Na_2CO_3, toluene/ethanol, reflux. (f) $AlLiH_4$, THF, 0 °C to RT. (g) TPAP, NMO, CH_2Cl_2, RT.

Scheme 4. Modified Benzene Core Ring Thienyl Dienoic Acids Synthesis[a]



[a] Reagents and conditions: (a) NIS, TsOH (10%), CH_2Cl_2. (b) Cs_2CO_3, R−Br, DMF, RT. (c) $Pd(PPh_3)_4$, 2-formylthiophene-3-boronic acid, toluene/ethanol, reflux. (d) Triethyl-3-methylphosphonocrotonate, *n*-BuLi, THF/DMPU, −78 °C to RT. (e) 2 N aq. LiOH, EtOH, reflux then HCl and recrystallization from CH_3CN.

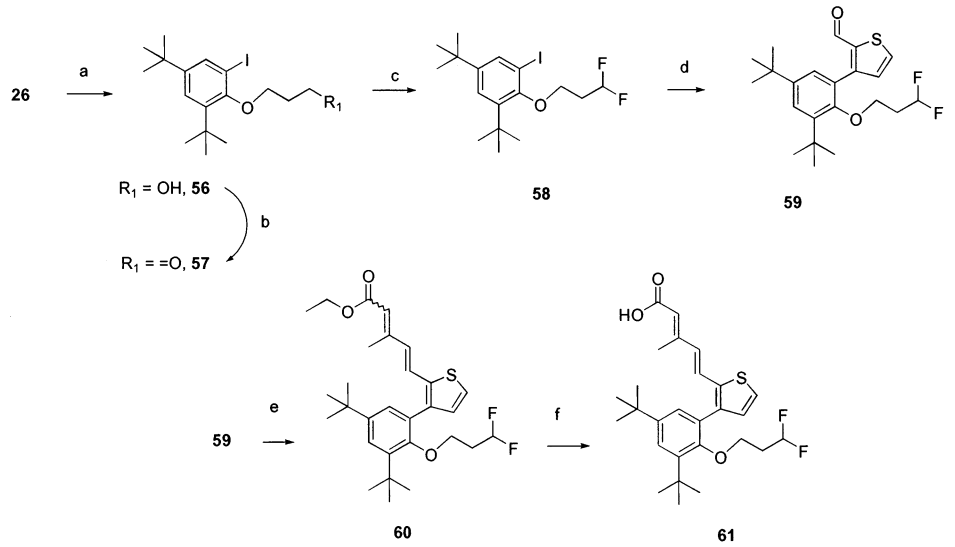
PPARγ heterodimer when used alone and in a synergistic manner when they are used in combination with a PPARγ ligand (e.g., BRL49653).[6] Other studies have shown that this in vitro observation translates into a similar in vivo effect.[6] In the case of RXR modulators (e.g., **4**, Table 4, entry 3), the RXR:PPARγ heterodimer activation is of a much lower amplitude than observed with RXR agonists. Ultimately, no activation of the RXR:PPARγ heterodimer is observed for full RXR antagonists (data not shown). Again, when the same RXR modulators are used in combination with a PPARγ agonist (e.g., BRL49653), a much cleaner response with a larger window of the activity was observed.[9]

To further characterize the compounds described in this communication, we used compounds both alone or in combination with BRL49653 to determine their RXR:PPARγ activation (Table 4).

Previous data have shown that RXR homodimer activity can be affected by elongation of the 6-alkoxy side-chain of this type of molecule.[9,26] As a general rule, a short side-chain (e.g., methoxy or ethoxy) produces RXR homodimer agonists, while a longer side-chain results in RXR homodimer antagonists. We have demonstrated that this activity can also be tuned by the use of fluorine in this particular side chain to produce a smooth transition between RXR homodimer agonist, partial agonist, and antagonist activity. The switch from agonist to antagonist typically happens between an ethoxy and a propoxy side-chain. While the same paradigm applies to the series of compounds presented in this communication,[27] we chose to focus on the synthesis and biological evaluation of selected examples of each series containing a 6-fluorinated alkoxy side chain.

Binding Data. All of the compounds shown in Table 3 bind with very high affinity to the RXR receptors α, β, and γ subtype. In fact, one of the compounds (**25b**) has sub-nanomolar affinity for RXRα, Table 3, entry 11). In general, the compounds described in Table 3 tend to exert some degree of selectivity for RXRα over RXRβ and RXRγ (exceptions are **31a**, **34**, **44**, **49,** and **55b**, Table 3, entries 7, 13, 14, 16, and 4, respectively). No RARβ or RARγ binding was observed (K_i > 5000 nM) with the exception of compounds **25c** and **44** which exhibit respective K_i values of 2221 and 1109 nM for RARγ (Table 3, entries 10 and 14) and compounds **31a**,

Scheme 5. 3,3-Difluoropropoxy Side Chain Synthesis[a]



[a] Reagents and conditions: (a) NaH, *tert*-butyldimethylsilyloxy-3-bromopropane, DMF, 0 °C, then TBAF in THF. (b) PCC/Celite/molecular sieve, CH_2Cl_2. (c) DAST, CH_2Cl_2 RT. (d) 2-Formylthiophene-3-boronic acid, Na_2CO_3, toluene/EtOH, reflux. (e) Triethyl-3-methyl phosphonocrotonate, *n*-BuLi, THF/DMPU, −78 °C to RT. (f) 2 N aq. LiOH, EtOH, reflux then HCl and recrystallization from CH_3CN.

Table 1. Hypoglycemic Activity of **4** in the *db*/*db* Mouse Model after 7 days of Dosing

compounds	lean control (mg/dL)	*db*/*db* control (mg/dL)	drug treated *db*/*db* (mg/dL)	% normalization vs BRL46953[a]
BRL 49653	205 ± 5	750 ± 15	412 ± 10	100
2	207 ± 5	740 ± 15	400 ± 5	101
4	203 ± 5	749 ± 10	409 ± 6	101

[a]BRL49653 used as reference compound for efficacy (100%).

Table 2. Triglycerides and T4 Levels Effect of **2** and **4** in Male Sprague Dawley Rats at 24 h

compounds	control	BRL 49653	**2**	**4**
triglycerides (mg/dL)	72 ± 10	78 ± 5	152 ± 10	75 ± 5
T4 (ng/mL)	73 ± 4	70 ± 3	37 ± 2	70 ± 5

44, and **49** that have respective K_i values of 4064, 2056, and 4742 nM for RARβ (Table 3, entries 7, 14, and 16). All of the compounds also have weak affinity for RARα (K_i > 1300 nM). None of the described compounds show any binding to PPARα. Evaluation of PPARγ activity showed that the majority of the compounds bind weakly (1750 < K_i < 6750 nM) or not at all, while two analogues **55a** and **55b** have K_i values of 1750 and 2607 nM, respectively (Table 3, entries 5 and 4 respectively), and are the only compounds with a K_i < 3000 nM for PPARγ.

Cotransfection Evaluation. When evaluated in the cotransfection assay, the compounds shown in Table 4 are potent RXR homodimer inhibitors with IC_{50} values ranging from 2 to 271 nM. The best compounds also exhibit >79% inhibition of the RXR homodimer. Only **25b** and **31a** show low efficacy (38 and 42% respectively, Table 4, entries 8 and 12) in the assay although both exhibit good potency (5.1 and 11.4 nM, respectively). Both compounds (**25b** and **31a**) possess a 2,2-difluoroethoxy side chain and show a partial agonist profile (16 and 17% efficacy, respectively) in the cotransfection assay. Compounds **39a** and **55a** also possess the same

Table 3. Binding Affinity of Compounds **25a**−**c**, **31a**−**c**, **34**, **39a**,**b**, **40**, **44**, **49**, **55a**,**b**, and **61** for RXRα, β, γ, RARα,β,γ, and PPARα,γ[a]

entries	compds	RXRα K_i (nm)	RXRβ K_i (nM)	RXRγ K_i (nM)	RARα K_i (nM)	RARβ K_i (nM)	RARγ K_i (nM)	PPARα K_i (nM)	PPARγ K_i (nM)
1	**2**	18 ± 1	20 ± 12	18 ± 11	>1000	>1000	>1000	>1000	>1000
2	**4**	3 ± 2	9 ± 4	12 ± 6	2745	4687	>1000	>10000	5590
3	**25a**	1.9 ± 0.2	6.0 ± 0.3	4.9 ± 0.1	1399	5623	>1000	>1000	3224
4	**55b**	9.9 ± 3.8	6.9 ± 2.3	4.9 ± 2.1	>10000	8064	>10000	>10000	1750
5	**55a**	3.2 ± 1.9	5.2 ± 3.0	6.9 ± 2.6	5650	8000	>10000	>10000	2607
6	**31b**	3.4 ± 0.8	2.9 ± 1.3	10.0 ± 3.4	3410	>10000	>10000	>10000	3151
7	**31a**	2.2 ± 1.5	1.6 ± 1.0	2.5 ± 1.3	2569	4064	>10000	>10000	3149
8	**39b**	15.2 ± 2.7	23.9 ± 8.2	48.6 ± 31.2	7500	>10000	>10000	>10000	>10000
9	**40**	20.9 ± 5.1	26.0 ± 4.3	154.7 ± 25.1	>10000	>10000	>10000	>10000	>10000
10	**25c**	1.9 ± 1.3	5.7 ± 2.3	7.6 ± 2.8	2481	8269	2221	>10000	4706
11	**25b**	0.9 ± 0.2	2.5 ± 1.4	1.9 ± 0.8	3726	>10000	>10000	>10000	4715
12	**39a**	29.6 ± 12.3	42.1 ± 15.3	73.9 ± 30.0	>1000	>10000	>10000	>10000	
13	**34**	6.2 ± 2.3	7.2 ± 2.3	6.6 ± 2.5	3671	>10000	>10000	>10000	4285
14	**44**	48.0 ± 25.4	51.5 ± 16.2	63.2 ± 31.0	>10000	2056	1109	>10000	>10000
15	**31c**	8.7 ± 2.7	15.1 ± 8.3	18.1 ± 6.5	3442	>10000	>10000	>10000	>10000
16	**49**	1.0 ± 0.8	0.9 ± 0.6	15.9 ± 11.0	8788	4742	>10000	>10000	6571
17	**61**	1.9 ± 0.9	5.3 ± 3.1	13.9 ± 4.1	5409	>10000	5409	>10000	6571

[a] K_i calculated using [^{3}H]-9-*cis*-RA for RXR, [^{3}H]-ATRA for RAR, and proprietary [^{3}H]-selective ligand for PPARα,γ. All data shown in nM.

Table 4. In Vitro Evaluation of RXR Modulators in CV-1 Cells. K_i Calculated Using [^{3}H]-9-*cis*-RA for RXR and [^{3}H]-ATRA for RAR[a]

entries	compds	RXRα agonist efficacy (%)	RXRα agonist EC_{50} (nM)	RXRα antagonist efficacy (%)	RXRα antagonist IC_{50} (nM)	RXRα/ PPARγ efficacy (%)	RXRα/ PPARγ EC_{50} (nM)	RXRα/ PPARγ synergy efficacy (%)	RXRα/ PPARγ synergy EC_{50} (nM)	RXR/ RAR synergy (fold)
1	**BRL49653**	NA	NA	NA	NA	100 ± 5	325 ± 15	NA	NA	NA
2	**2**	70 ± 21	11 ± 10	12	0	62	99 ± 11	166 ± 57	38 ± 20	7.0
3	**4**	4 ± 2	NC	84 ± 10	8.0 ± 4.2	11	131.5 ± 25.6	60 ± 29	3 ± 1	2.0
4	**25a**	15 ± 6	NC	72 ± 6	4.5 ± 3.2	43 ± 10	19.2 ± 27.3	140 ± 36	4.4 ± 1.3	1.9
5	**55b**	3 ± 1	NC	83 ± 3	10.3 ± 5.7	45 ± 11	202.6 ± 36.0	76 ± 19	13.6 ± 7.1	1.9
6	**55a**	8 ± 2	NC	61 ± 13	15.5 ± 10.5	44 ± 6	556.2 ± 251.6	89 ± 36	15.3 ± 9.2	3.1
7	**31b**	3 ± 1	NC	79 ± 5	6.8 ± 3.4	55 ± 14	623.9 ± 365.8	141 ± 21	37.1 ± 14.7	1.8
8	**31a**	17 ± 3	NC	42 ± 7	11.4 ± 0.1	52 ± 12	1716.1 ± 375.3	145 ± 3	117.4 ± 34.8	3.0
9	**39b**	1 ± 1	NC	87 ± 2	49.6 ± 32.3	20 ± 5	736.7 ± 303.1	69 ± 12	54.2 ± 12.6	1.4
10	**40**	0 ± 0	NC	88 ± 1	46.3 ± 2.4	2 ± 1	NC	23 ± 12	23.8 ± 12.1	1.5
11	**25c**	2 ± 1	NC	80 ± 5	3.3 ± 1.6	52 ± 7	1604.0 ± 303.4	131 ± 36	4.6 ± 2.5	2.1
12	**25b**	16 ± 3	NC	38 ± 6	5.1 ± 0.7	59 ± 6	8.8 ± 4.3	181 ± 10	2.4 ± 0.6	3.5
13	**39a**	3 ± 1	NC	81 ± 1	79.9 ± 47.2	23 ± 8	1723.8 ± 206.7	104 ± 11	155.8 ± 91.5	1.6
14	**34**	5 ± 3	NC	77 ± 11	11.6 ± 7.7	51 ± 17	173.6 ± 30.8	207 ± 30	26.0 ± 3.7	2.5
15	**44**	2 ± 0	NC	89 ± 1	271.2 ± 80.3	28 ± 5	1272.7 ± 310.4	65 ± 19	136.6 ± 44.5	2.3
16	**31c**	3 ± 0	NC	87 ± 2	10.4 ± 10.5	45 ± 3	110.0 ± 36.9	117 ± 19	12.4 ± 6.4	2.0
17	**49**	13 ± 7	NC	79 ± 1	2.3 ± 1.9	43 ± 13	802.0 ± 299.1	128 ± 25	7.1 ± 6.6	3.1
18	**61**	0 ± 0	NC	93 ± 1	8.7 ± 3.2	16 ± 5	508.7 ± 150.2	66 ± 5	15.0 ± 10.6	1.9

[a] RXR:PPARγ synergy mode calculated using 100 nM of BRL49653, efficacy relative to BRL49653. RXR:RAR synergy calculated using 3 nM of TTNPB, fold elevation over DMSO background. NA: no activity, NC: not calculated. All data shown in nM.

2,2-difluoroethoxy side chain but associated to a different locked-trienoic acid (phenyl instead of thienyl or cyclopentyl for **39a**) or a different benzene core ring (3-ethyl instead of 3-isopropyl for **55a**). Unlike **25b** and **31a**, **39a** and **55a** (Table 4, entries 13 and 6, respectively) display a full RXR homodimer antagonists profile. Moreover, many of the compounds represented in Table 4 can activate the RXR:PPARγ heterodimer when used alone. This result contrasts with the reported activity of compounds belonging to the trienoic acid series represented by **4** (Figure 2 and Table 4, entry 3) which show very low efficacy on the RXR:PPARγ heterodimer when they are tested alone. However, only **25a** and **25b** showed EC_{50} values below 20 nM, Table 4, entries 4 and 12) while maintaining reasonable efficacy (43−59%). Many of the other compounds were considerably less potent ($110 < EC_{50} < 1604$ nM) but showed reasonably high efficacy >50%).

As expected, the concomitant use of the RXR ligands with BRL49653 produces a much greater response in the RXR:PPARγ heterodimer assay than RXR or BRL49653 ligands used alone. All showed a synergistic increase in efficacy and potency response with the exception of **31a**, **39a**, and **44** ($EC_{50} > 100$ nM, Table 4, entries 8, 13, and 15). For example, compounds **25c** and **49** (Table 4, entries 11 and 17) show an increase in efficacy from 52 and 43%, to 131 and 117%, respectively. This was also accompanied by an impressive increase in the potency from 1604 and 802 nM to 4.6 and 7.1 nM, respectively. With the exception of **40** (Table 4, entry 10), all the compounds from Table 4 showed similar or better synergystic RXR:PPARγ response than our lead compound **4**.

In our previous communication, we described an RXR:RAR synergy assay as a measure of potential side effects associated with RAR activation. We used the RXR test compound in combination with an EC_{30} of a potent RAR agonist (TTNPB), a concentration which could produce a synergistic response. The results showed that compounds such as **4** dramatically decreased activation of the RXR:RAR heterodimer compared to classic RXR agonists such as **2** when evaluated in a synergy mode (Table 4, entries 2 and 3). Similarly, we characterized the compounds from this communication using the RXR:RAR synergy assay. Results described as fold induction over DMSO background are collected in Table 4. While the RXR:RAR synergy closely correlated with the agonist activity in the trienoic acid series (exemplified by **4**),[9] it clearly appeared that the locked derivatives show a different profile in that assay. Most of the compounds show reduced synergistic activity (<2-fold, Table 4, entries 4, 5, 7, 9, 10, 13, 16, and 18, respectively, compounds **25a**, **55b**, **31b**, **39b**, **40**, **39a**, **31c**, and **49**). However, compounds such as **55a**, **31a**, **25b**, **34**, **44**, and **49** show some level of RXR:RAR synergy (2.3<fold< 3.5, Table 4, entries 6, 8, 12, 14, 15, and 17) while retaining similar RXR homodimer antagonist activity.

Interestingly, for a given alkoxy side-chain, the RXR homodimer activity can be modulated using different locking structures and/or introducing different benzene ring substitution patterns. For example, **25b**, **31a**, **39a**, and **55a** possess the same 2,2-difluoroethoxy side chain, but **39a** shows no RXR homodimer activation, while **25b** and **31a** show weak RXR homodimer activation (Table 4, entries 4, 8, 13, and 6). Although 3**9a** and **55a** share the same 3,5-di-*iso*-propyl-6-(2,2-difluoroethoxy)benzene scaffold, **39a** possesses a phenyl-locked structure instead of a cyclopentyl or thienyl-locked moiety and is an RXR homodimer activator, whereas **55a** possesses a thienyl-trienoic acid moiety (same pattern as **31a**) combined with a 2-ethyl-5-*tert*-butylphenyl core instead of a 3,5-di-*iso*-propyl core and does not activate the RXR homodimer.

Discussion

From these structure activity relationship studies it is apparent that the trienoic acid scaffold can be replaced with a variety of locked-trienoic acid moieties (cycloalkyl, aromatic, and heteroaromatic) without severe loss of RXR activity or RXR selectivity. Cyclopentyl and thienyl-locked trienoic acids are better replacements of the trienoic acid moiety than phenyl and pyridine-locked compounds which consistently show weaker affinity for the RXR receptor (however, still in

the low nanomolar). This is probably due to a slight change in the tortional angle between the locked-trienoic acid and the aromatic scaffold. Previous communications have shown that this angle is critical for RXR activity.[28] Interestingly, we found that the cyclopentyl-trienoic acids are significantly less chemically stable than the parent trienoic acid whereas thienyl, phenyl, and pyridyl-trienoic acids display a comparable or better chemical stability relative to the reference trienoic acids.[29] Nearly all of the compounds from Table 4 show weak activation (<2-fold) of the RXR:RAR heterodimer when used in combination with 3 nM of an RAR agonist (e.g., TTNPB) except **49**, **31a**, **25b**, **34**, and **55a** (Table 4, entries 17, 8, 12, 14, and 6, respectively) which show greater than 2-fold activation. In most of the cases, the RXR:RAR synergy observed is comparable or lower than that measured with **4**.

To synthesize these compounds, we constructed complex molecules in relatively few steps using simple and reproducible chemical reactions including transition metal catalysis (Suzuki coupling), phenol alkylation, Horner-Wadsworth-Emmons reaction and saponification. Fluorinated alkoxy side chains were introduced using procedures previously described, except for compound **61**. Due to the unavailability of the 3-bromo-1,1-difluoropropane, we introduced this particular side chain at an earlier stage of the synthesis. Although each intermediate can be purified by silica gel chromatography, in most of the cases, the whole synthetic sequence could be performed using minimal purification over a silica plug for each intermediate, with crystallization of the final dienoic-acids from CH_3CN. Most of the intermediates including **16**, **20**, **26**, and **41** are chemically stable and can be stored for several months.

Conclusion

In summary, we have described the synthesis and structure activity relationship studies of a new series of locked-trienoic acids based on the 3,5-dialkyl-6-fluoroalkoxybenzene scaffold. These compounds represent a second generation of RXR-selective modulators which possess high affinity for the RXRs, are synergistic with PPARγ when used in combination with PPARγ agonists, and in most cases show reduced synergy on the RXR:RAR heterodimer when used in combination with an RAR agonist. We demonstrated that the trienoic acid scaffold can be successfully replaced with various locked-trienoic acids such as cyclopentyl, phenyl, thienyl, furyl, and pyridyl-trienoic acids, the best replacements being the cyclopentyl and thienyl-locked trienoic acids. The thienyl scaffold was particularly attractive because the synthetic route employed to make thienyl derivatives used the commercially available 2-formylthiophene-3-boronic acid and simple alkylated iodo- or bromophenols. This provided us with a versatile synthetic tool which was used to rapidly and conveniently transform a wide variety of substituted phenols into potent RXR ligands. **55a** and **55b** are representative examples of highly selective RXR modulators that can be synthesized in only five steps from the inexpensive phenol **50**.

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 Merck TLC glass plate precoated with silica gel F254 (0.2-mm thick). Flash chromatography was performed using Merck silica gel 60. HPLC of the final carboxylic acids were realized on a KROMASIL column (C18 100 Å, 5 μM) using reverse phase (eluent: MeOH/H_2O + 0.1% TFA).

2,4-Di-*iso*-propyl-6-iodophenol (16). To a solution of 52.2 g (0.293 mol) of **15** and 5.6 g (0.029 mol) of *p*-toluenesulfonic acid in 300 mL of CH_2Cl_2 was added 72.6 g (0.322 mol) of *N*-iodosuccinimide (NIS) portionwise at room temperature. After complexion of the reaction (TLC monitored), 200 mL of a 10% aqueous $Na_2S_2O_3$ was added and the mixture was stirred until the aqueous layer became milky. After separation, the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the organic layers were combined and dried over $MgSO_4$. After filtration and concentration, the residue was purified over silica gel (eluent: ethyl acetate/hexane, 5/95) to afford 89.1 g (0.29 mol, yield: 99%) of **16** as a deep red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 2.1 Hz, 1H), 7.00 (d, J = 2.0 Hz, 1H), 4.83 (s, 1H), 3.28 (heptet, J = 6.9 Hz, 1H), 2.80 (heptet, J = 6.9 Hz, 1H), 1.23 (d, J = 6.8 Hz, 6H), 1.21 (d, J = 6.8 Hz, 6H).

3,5-Di-*iso*-propyl-6-methoxymethoxy Iodophenol (17). To a slurry of sodium hydride (1.6 g, 0.04 mol) dissolved in 225 mL of anhydrous *N*,*N*-dimethyl-formamide (DMF) in a flame dried 500 mL round-bottom flask at 0 °C was added dropwise 10.0 g (0.033 mol) of **16** in 25 mL of DMF. The mixture was stirred at 0 °C for 30 min followed by dropwise addition of 3.22 g (0.04 mol) of methyl chloromethyl ether. The resultant reaction mixture was allowed to warm to ambient temperature and stirred for 3.0 h. The contents of the flask were poured into iced brine (200 mL) and stirred for 0.5 h. The aqueous layer was extracted with diethyl ether (2 × 200 mL) and the organic layers were combined, washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure. The concentrated product was filtered through a silica gel plug (eluting with diethyl ether) and concentrated under reduced pressure to give 11.3 g (0.032 mol, yield: 97%) of **17** as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 1.8 Hz, 1H), 7.06 (d, J = 1.8 Hz, 1H), 5.05 (s, 2H), 3.65 (s, 3H), 3.40 (heptet, J = 6.9 Hz, 1H), 2.81 (heptet, J = 6.9 Hz, 1H), 1.26 (d, J = 6.5 Hz, 6H), 1.21 (d, J = 6.6 Hz, 6H).

3,5-Di-*iso*-propyl-6-(methoxymethoxy)benzene Boronic Acid (18). To 10.0 g (0.029 mol) of compound **17** dissolved in 150 mL of a 1:2 mixture of diethyl ether-THF in a flame dried 300 mL round-bottom flask at −78 °C was added 21.9 mL (0.035 mol) of a 1.6 M solution of *n*-BuLi in hexanes. The mixture was stirred at −78 °C for 20 min followed by addition of 6.6 mL (0.058 mol) of trimethyl borate in one portion via syringe. The resultant mixture is allowed to stir at −78 °C for 0.5 h, warmed to ambient temperature, and stirred for a further 2 h. Thirty milliliters of aqueous 1 N HCl was added and the mixture stirred for an additional 0.5 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 30 mL). The organic layers were combined, washed (water, then 10% aqueous $Na_2S_2O_3$, then brine), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/EtOAc, 9:1) yielded 6.6 g (0.025 mol, yield: 86%) of **18** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 2.3 Hz, 1H), 7.23 (d, J = 2.3 Hz, 1H), 5.94 (s, 2H), 5.00 (s, 2H), 3.57 (s, 3H), 3.21 (heptet, J = 6.9 Hz, 1H), 2.89 (heptet, J = 6.9 Hz, 1H), 1.25 (d, J = 6.9 Hz, 6H), 1.24 (d, J = 6.9 Hz, 6H).

Ethyl-2-[3,5-di-*iso*-propyl-6-(methoxymethoxy)benzene] cyclopentene-1-carboxylate (19). To 6.6 g (0.025 mol) of **18** dissolved in 300 mL of 1:1 toluene-ethanol in a 500 mL round-bottom flask, was added 7.86 g (0.027 mol) of ethyl-2-(trifluoromethylsulfonyloxy)-1-cyclopentene-1-carboxylate, 5.3 g (0.05 mol) of 2 N aqueous Na_2CO_3 and 2.89 g (0.0025 mol) of $Pd(PPh_3)_4$. The reaction mixture was heated to 90 °C for 15.0 h, then cooled to room temperature, poured into brine (200 mL), and stirred for 0.3 h. The aqueous layer was extracted with EtOAc (2 × 200 mL) and the organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 9:1 hexanes−EtOAc) gave 8.0 g (0.022 mol, yield: 89%) of **19** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 2.2 Hz, 1H), 6.77 (d, J = 2.2 Hz, 1H), 4.81 (s, 2H), 3.98 (q, J = 7.1 Hz, 2H), 3.49 (s, 3H), 3.38 (heptet, J = 6.9 Hz, 1H), 2.82 (m, 5H), 1.99 (m, 2H), 1.22 (d, J = 6.8 Hz, 6H), 1.21 (d, J = 6.8 Hz, 6H), 0.95 (t, J = 7.1 Hz, 3H).

3,4-Cyclopentenyl-6,8-di-*iso*-propylcoumarin (20). To 8.0 g (0.022 mol) of **19** dissolved in 150 mL of THF in a 300 mL round-bottom flask was added 6 N aqueous HCl (25.0 mL, 0.15 mol). The resulting mixture was stirred at ambient temperature for 65.0 h. After such time, the solvent was removed under reduced pressure and the residue was taken up in water (100 mL). The aqueous layer was extracted with EtOAc (2 × 100 mL) and the organic layers were combined, washed (water then brine), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 9:1 hexanes−EtOAc) gave 5.9 g (0.022 mmol, yield: 99%) of coumarin **20** as a yellow-orange oil which solidified upon standing. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 1.7 Hz, 1H), 7.10 (d, J = 1.8 Hz, 1H) 3.65 (heptet, J = 6.9 Hz, 1H), 3.08 (t, J = 7.6 Hz, 2H), 2.93 (m, 3H), 2.21 (m, 2H), 1.29 (d, J = 7.4 Hz, 6H), 1.28 (d, J = 7.2 Hz, 6H).

2-[3,5-Di-*iso*-propyl-6-hydroxybenzene]cyclopentene-1-methanol (21). To 2.0 g (7.4 mmol) of coumarin **20** dissolved in 75 mL of anhydrous THF in a flame dried 200 mL round-bottom flask at 0 °C was added 400 mg (7.4 mmol) of $NaAlH_4$ portion-wise. The resultant mixture is allowed to warm to ambient temperature and stirred for 4.0 h. After such time, water (0.14 mL, 7.4 mmol) was added, followed by 6 N aqueous sodium hydroxide (2.5 mL, 14.8 mmol). The resultant mixture was allowed to stir for 0.5 h, filtered through a plug of silica gel (eluting with diethyl ether) and concentrated under reduced pressure to give 2.0 g (7.3 mmol, yield: 99%) of **21** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, J = 2.1 Hz), 6.75 (d, J = 2.2 Hz, 1H), 5.55 (s, 1H), 5.07 (s, 2H), 3.29 (heptet, J = 6.9 Hz, 1H), 2.82 (heptet, J = 6.9 Hz, 1H), 2.70 (m, 4H), 2.02 (m, 2H), 1.62 (broad s, 1H), 1.25 (d, J = 6.9 Hz, 6H), 1.22 (d, J = 7.1 Hz, 6H).

1-(3,5-Di-*iso*-propyl-6-propoxybenzene)cyclopentene-2-methanol (22a). To 2.0 g (7.3 mmol) of **21** dissolved in 75 mL of anhydrous DMF in a flame dried 200 mL round-bottom flask, was added 1.00 g (8.1 mmol) of 1-bromopropane followed by 4.5 g (29.6 mmol) of CsF. The mixture was allowed to stir at room temperature for 18 h. Water (100 mL) was added and the mixture was allowed to stir for an additional 0.5 h. The aqueous layer was extracted with EtOAc (2 × 100 mL), and the organic layers were combined, washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by silica gel flash column chromatography (eluent: 9/1 hexanes−EtOAc) yielded 2.15 g (6.79 mmol, yield: 93%) of **22a** as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, J = 2.2 Hz, 1H), 6.78 (d, J = 2.2 Hz, 1H), 3.98 (d, J = 5.0 Hz, 2H), 3.57 (t, J = 6.7 Hz, 2H), 3.32 (heptet, J = 6.9 Hz, 1H), 2.84 (heptet, J = 6.9 Hz, 1H), 2.74 (t, J = 7.3 Hz, 2H), 2.64 (t, J = 7.3 Hz, 2H), 2.00 (m, 2H), 1.71 (m, 2H), 1.22 (d, J = 6.9 Hz, 6H), 1.17 (d, J = 6.9 Hz, 6H), 0.97 (t, J = 7.4 Hz, 3H).

1-(3,5-Di-*iso*-propyl-6-hydroxybenzene)-2-formylcyclopentene (23a). To 2.15 g (6.80 mmol) of **22a** dissolved in 70 mL of anhydrous CH_2Cl_2 in a flame dried 200 mL round-bottom flask, was added 1.19 g (10.2 mmol) of 4-methylmorpholine-*N*-oxide (NMO) followed by 0.119 g (0.34 mmol) of tetrapropylammonium perruthenate (TPAP). The resulting mixture was stirred at ambient temperature for 1.5 h. After such time, the reaction mixture was filtered through a plug of silica gel (eluting with CH_2Cl_2) and concentrated under reduced pressure to yield 2.13 g (6.21 mmol, yield: 91%) of **23a** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.11 (d, J = 2.1 Hz, 1H), 6.85 (d, J = 2.0 Hz, 1H), 3.55 (t, J = 6.4 Hz, 2H), 3.33 (heptet, J = 6.9 Hz, 1H), 2.99 (t, J = 7.4 Hz, 2H), 2.87 (heptet, J = 6.9 Hz, 1H), 2.72 (t, J = 7.5 Hz, 2H), 2.03 (m, 2H), 1.67 (m, 2H), 1.28 (d, J = 7.1 Hz, 6H), 1.23 (d, J = 7.0 Hz, 6H), 0.96 (t, J = 7.4 Hz, 3H).

Ethyl-(*2E*,*4E*)-3-methyl-6,7-cyclopentenyl-7-(3,5-di-*iso*-propyl-6-propoxybenzene) Pentanedienoate (24a). To 5.38 g (20.4 mmol) of triethyl 3-methyl-4-phosphonocrotonate dissolved in 60.0 mL of a 1:2 mixture of THF-DMPU in a flame dried 200 mL round-bottom flask at −78 °C, was added dropwise 13.6 mL (21.7 mmol) of 1.6 M *n*-BuLi in hexanes. The mixture was allowed to stir for 20 min followed by dropwise addition of 2.33 g (6.80 mmol) of aldehyde **23a** in 10 mL of a 1:2 THF-DMPU solution. The reaction mixture was allowed to stir at −78 °C for 0.5 h, warmed to ambient temperature, and stirred for an additional 2 h. Water (100 mL) was added and the mixture was stirred for 0.5 h. The aqueous layer was separated and extracted with EtOAc (2 × 100 mL), and the organic layers were combined, washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 9:1 hexanes−EtOAc) gave 2.74 g (6.45 mmol, yield: 95%) of ester **24a** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 2.2 Hz, 1H), 6.85 (d, J = 15.8 Hz, 1H) 6.79 (d, J = 2.2 Hz, 1H), 6.21 (d, J = 15.8 Hz, 1H), 5.79 (s, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.53 (t, J = 6.5 Hz, 2H), 3.34 (heptet, J = 6.9 Hz, 1H), 2.86 (m, 3H), 2.66 (t, J = 7.3 Hz, 2H), 2.22 (s, 3H), 2.01 (m, 2H), 1.65 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H) 1.24 (d, J = 7.0 Hz, 6H), 1.23 (d, J = 6.8 Hz, 6H), 0.95 (t, J = 7.4 Hz, 3H).

(*2E*,*4E*)-3-Methyl-6,7-cyclopentenyl-7-(3,5-di-*iso*-propyl-6-propoxybenzene) pentanedienoic Acid (25a). To 2.74 g (6.45 mmol) of ester **24a** dissolved in 75 mL of ethanol in a 200 mL round-bottom flask was added 10 mL (20.0 mmol) of a 2 M aqueous LiOH solution. The mixture was heated to 90 °C for 3.0 h, then cooled and concentrated under reduced pressure. The residue was taken up in 100 mL of 1 N aqueous HCl and the flask was shaken for 1 min. The resultant suspension was extracted with EtOAc (2 × 100 mL) and the organic layers were combined, washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure. The concentrate was filtered through a short plug of silica gel (eluting with EtOAc), concentrated under reduced pressure and crystallized from acetonitrile to give 2.41 g (5.68 mmol, yield: 88%) of corresponding acid **25a** as light yellow crystals (mp = 134.1−135.4 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 2.1 Hz, 1H), 6.90 (d, J = 15.8 Hz, 1H) 6.79 (d, J = 2.1 Hz, 1H), 6.23 (d, J = 15.7 Hz, 1H), 5.81 (s, 1H), 3.53 (t, J = 6.5 Hz, 2H), 3.33 (heptet, J = 6.9 Hz, 1H), 2.88 (m, 3H), 2.66 (t, J = 7.3 Hz, 2H), 2.23 (s, 3H), 2.03 (m, 2H), 1.65 (m, 2H), 1.24 (d, J = 6.8 Hz, 6H), 1.23 (d, J = 6.9 Hz, 6H), 0.95 (t, J = 7.4 Hz, 3H). Anal. ($C_{26}H_{36}O_3$); C: calcd, 78.75, found, 78.24; H: calcd, 9.15, found, 9.31. MS (EI, 70 eV) 396 *m*/*z* 396 (MH^+, 100), 396 (100), 378 (30). 296 (30). HRMS for $C_{26}H_{37}O_3$ (MH^+): calcd, 396.2664; found, 396.2870.

1-[3,5-Di-*iso*-propyl-6-(2,2-difluoroethoxy)benzene] cyclopentene-2-methanol (22b). 22b was synthesized from 0.152 g (0.56 mmol) of **21** and 0.097 g (0.67 mmol) of 1-bromo-2,2-difluoroethane in the presence of 0.54 g (1.7 mmol) of CsF according to the procedure described for the synthesis of **22a**. 0.163 g (0.48 mmol, yield: 87%) of **22b** was isolated as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 2.2 Hz, 1H), 6.80 (d, J = 2.2 Hz, 1H), 5.97 (tt, J = 55.2, 4.1 Hz, 1H), 4.07 (d, J = 4.4 Hz, 2H), 3.85 (dt, J = 13.9, 4.1 Hz, 2H), 3.31 (heptet, J = 6.9 Hz, 1H), 2.85 (heptet, J = 6.9 Hz, 1H), 2.74 (t, J = 7.3 Hz, 2H), 2.65 (t, J = 7.4 Hz, 2H), 2.01 (m, 2H), 1.23 (d, J = 6.8 Hz, 6H), 1.22 (d, J = 6.8 Hz, 6H).

1-[3,5-Di-*iso*-propyl-6-(3-fluoropropoxy)benzene] cyclopentene-2-methanol(22c). 22c was synthesized from 0.51 g (1.8 mmol) of **21** and 0.31 g (2.2 mmol) of 1-bromo-2,2-

difluoroethane in the presence of 1.8 g (5.6 mmol) of CsF according to the procedure described for the synthesis of **22a**. 0.53 g (1.6 mmol, yield: 85%) of **22c** was isolated as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 2.1 Hz, 1H), 6.78 (d, J = 2.2 Hz, 1H), 4.63 (dt, J = 47.1, 5.7 Hz, 2H), 4.02 (d, J = 5.4 Hz, 2H), 3.75 (t, J = 6.2 Hz, 2H), 3. (heptet, J = 6.9 Hz, 1H), 2.84 (heptet, J = 6.9 Hz, 1H), 2.74 (t, J = 7.2 Hz, 2H), 2.64 (t, J = 7.3 Hz, 2H), 2.20 (t, J = 5.9 Hz, 1H), 2.09 (m, 2H), 1.99 (m, 2H), 1.23 (d, J = 6.8 Hz, 6H), 1.22 (d, J = 6.9 Hz, 6H).

1-[3,5-Di-*iso*-propyl-6-(2,2-difluoroethoxy)benzene]-2-formylcyclopentene (23b). **23b** was synthesized from 0.163 g (0.48 mmol) of **22b** and 0.08 g (0.72 mmol) NMO in the presence of 0.008 g (0.024 mmol) of TPAP according to the procedure described for the synthesis of **23a**. 0.162 g (0.48 mmol, yield: 100%) of **23b** was isolated as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.14 (d, J = 2.1 Hz, 1H), 6.88 (d, J = 2.2 Hz, 1H), 5.93 (tt, J = 55.0, 4.0 Hz, 1H), 3.83 (dt, J = 13.6, 3.9 Hz, 2H), 3.31 (heptet, J = 6.9 Hz, 1H), 2.98 (t, J = 7.4 Hz, 2H), 2.88 (heptet, J = 6.9 Hz, 1H), 2.74 (t, J = 4.5 Hz, 2H), 2.05 (m, 2H), 1.24 (d, J = 7.0 Hz, 6H), 1.23 (d, J = 6.9 Hz, 6H).

1-[3,5-Di-*iso*-propyl-6-(3-fluoropropoxy)benzene]-2-formylcyclopentene (23c). **23c** was synthesized from 0.53 g (1.6 mmol) of **22c** and 0.28 g (2.4 mmol) of NMO in the presence of 0.03 g (0.08 mmol) of TPAP according to the procedure described for the synthesis of **23a**. 0.52 g (1.6 mmol, yield: 100%) of **23c** was isolated as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.12 (d, J = 2.2 Hz, 1H), 6.87 (d, J = 2.2 Hz, 1H), 4.58 (dt, J = 47.1, 5.7 Hz, 2H), 3.71 (t, J = 5.9 Hz, 2H), 3.28 (heptet, J = 6.9 Hz, 1H), 2.98 (t, J = 7.5 Hz, 2H), 2.87 (heptet, J = 6.9 Hz, 1H), 2.73(t, J = 7.6 Hz, 2H), 2.01 (m, 4H), 1.24 (d, J = 6.9 Hz, 12H).

Ethyl-(*2E*,*4E*,*6Z*)-3-methyl-6,7-cyclopentenyl-7-[3,5-di-*iso*-propyl-6-(2,2-difluoro ethoxybenzene] pentane-2,4,6-trienoate (24b). Reaction of 0.162 mg (0.48 mmol) of **23b** in the presence of the anion of triethyl-3-methyl-phosphonocrotonate (generated from 0.35 mL, 1.4 mmol of of triethyl-3-methyl-phosphonocrotonate and 0.97 mL of *n*BuLi in hexanes 2.5 M in THF-DMPU, 1.5 mmol) according to the procedure described for the synthesis of **24a** affords 0.202 g (0.45 mmol, yield: 93%) of the corresponding ester **24b** as a mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, J = 2.1 Hz, 1H), 6.82 (d, J = 2.3 Hz, 1H), 6.79 (d, J = 16.0 Hz, 1H), 6.24 (d, J = 15.8 Hz, 1H), 5.90 (tt, J = 55.4, 4.8 Hz, 1H), 5.81 (s, 1H), 4.17 (q, J = 7.0 Hz, 2H), 3.80 (dt, J = 13.8, 4.0 Hz, 2H), 3.31 (heptet, J = 6.9 Hz, 1H), 2.87 (m, 3H), 2.68 (t, J = 7.3 Hz, 2H), 2.21 (s, 3H), 2.03 (m, 4H), 1.28 (t, J = 6.8 Hz, 3H), 1.25 (d, J = 6.8 Hz, 6H), 1.24 (d, J = 6.8 Hz, 6H).

Ethyl-(*2E*,*4E*,*6Z*)-3-methyl-6,7-cyclopentenyl-7-[3,5-di-*iso*-propyl-6-(3-fluoro propoxy)benzene]pentane-2,4,6-trienoate (24c). Reaction of 0.52 g (1.6 mmol) of **23c** in the presence of the anion of triethyl-3-methyl-phosphonocrotonate (generated from 1.15 mL, 4.7 mmol of triethyl-3-methyl-phosphonocrotonate, and 3.2 mL of *n*BuLi in hexanes 2.5 M in THF-DMPU 15.8 mL) according to the procedure described for the synthesis of **24a** affords 657 mg (1.5 mmol, yield: 94%) of the corresponding ester **24c** as a mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 2.1 Hz, 1H), 6.82 (d, J = 15.7 Hz, 1H), 6.81 (d, J = 2.2 Hz, 1H), 6.22 (d, J = 15.8 Hz, 1H), 5.80 (s, 1H), 4.58 (dt, J = 47.1, 5.8 Hz, 2H), 4.15 (q, J = 6.9 Hz, 2H), 3.69 (t, J = 5.9 Hz, 2H), 3.29 (heptet, J = 6.9 Hz, 1H), 2.86 (m, 3H), 2.67 (t, J = 7.4 Hz, 2H), 2.21 (s, 3H), 2.07 (m, 4H), 1.26 (t, J = 7.2 Hz, 3H), 1.25 (d, J = 6.8 Hz, 6H), 1.24 (d, J = 6.8 Hz, 6H).

(*2E*,*4E*,*6Z*)-3-Methyl-6,7-cyclopentenyl-7-[3,5-di-*iso*-propyl-6-(2,2-difluoroethoxy) benzene]pentane-2,4,6-trienoic Acid (25b). Saponification of 0.202 g (0.45 mmol) of **24b** in the presence of 0.70 mL of LiOH (2 M aqueous solution) in a 1/1 mixture of THF/MeOH (2.5/2.5 mL) according to the procedure described for the synthesis of **25a** affords 87.7 mg (0.21 mmol, yield: 47%) of the desired acid **25b** as a single stereoisomer (off white solid, mp = 162.3−165.1 °C, CH_3CN). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 2.0 Hz, 1H), 6.83 (d, J = 14.9 Hz, 1H), 6.81 (d, J = 2.3 Hz, 1H), 6.25 (d, J = 15.8 Hz, 1H), 5.99 (tt, J = 56.8, 4.8 Hz, 1H), 5.83 (s, 1H), 3.71 (t, J = 5.8 Hz, 2H), 3.24 (heptet, J = 6.9 Hz, 1H), 2.86 (m, 3H), 2.69 (t, J = 7.2 Hz, 2H), 2.21 (s, 3H), 2.10 (m, 4H), 1.24 (d, J = 6.9 Hz, 6H), 1.23 (d, J = 6.8 Hz, 6H). Anal. ($C_{25}H_{32}F_2O_3$) C, H. MS (EI, 70 eV) 418 *m*/*z* 418 (MH^+, 90), 435 (100), 418 (90), 400 (80), 372 (85), 358 (45). HRMS for $C_{25}H_{33}F_2O_3$ (MH^+); calcd, 418.2320, found, 418.2435.

(*2E*,*4E*,*6Z*)-3-Methyl-6,7-cyclopentenyl-7-[3,5-di-*iso*-propyl-6-(3-fluoropropoxy) benzene]pentane-2,4,6-trienoic Acid (25c). Saponification of 657 mg (1.5 mmol) of **24c** in the presence of 2.3 mL of LiOH (2 M aqueous solution) in a 1/1 mixture of THF/MeOH (7.5/7.5 mL) according to the procedure described for the synthesis of **25a** affords 499.0 mg (1.21 mmol, yield: 81%) of the desired acid **25c** as a single stereoisomer (off white solid, mp 151.3−153.2 °C, CH_3CN). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 2.2 Hz, 1H), 6.86 (d, J = 15.8 Hz, 1H), 6.81 (d, J = 2.2 Hz, 1H), 6.24 (d, J = 15.7 Hz, 1H), 5.82 (s, 1H), 4.57 (dt, J = 47.1, 5.8 Hz, 2H), 3.69 (t, J = 5.9 Hz, 2H), 3.28 (heptet, J = 6.9 Hz, 1H), 2.86 (m, 3H), 2.68 (t, J = 7.4 Hz, 2H), 2.22 (s, 3H), 2.00 (m, 4H), 1.25 (d, J = 6.9 Hz, 6H), 1.24 (d, J = 6.8 Hz, 6H). Anal. ($C_{26}H_{35}FO_3 \cdot 0.2\ H_2O$); C, H. MS (EI, 70 eV) 414 *m*/*z* 414 (MH^+, 100), 414 (100), 396 (98), 368 (70), 354 (80). HRMS for $C_{26}H_{36}FO_3$ (MH^+); calcd, 414.2570, found: 414.2635.

2,4-Di-*tert*-butyl-6-iodophenol (26). Iodination of 50.0 g (0.24 mol) of 2,4-di*tert*-butylphenol in the presence of 65.4 g (0.29 mol) of NIS and 4.6 g (0.024 mol) of *p*-toluenesulfonic acid using the procedure described for the synthesis of **16** affords 76.4 g (0.23 mol, yield: 96%) of 2,4-di*tert*butyl-6-iodophenol **26** as a pale yellow solid (mp = 76.3−77.6 °C -methanol-). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 2.1 Hz, 1H), 7.27 (d, J = 2.1 Hz, 1H), 5.35 (s, 1H), 1.39 (s, 9H), 1.27 (s, 9H).

3,5-Di-*iso*-propyl-6-(2,2-difluoroethoxy) iodobenzene (27a). To a solution of 250 mg (0.82 mmol) of **16** and 131 mg (0.91 mmol) of 1-bromo-2,2-difluoroethane in 10.0 mL of dry DMF was added 402 mg (1.2 mmol) of Cs_2CO_3 at room temperature. The mixture was stirred overnight at room temperature and water was added (15.0 mL). The solution was extracted twice with ethyl acetate and the organic layers were washed (with water and brine successively) and dried ($MgSO_4$). After concentration, the residue was purified over silica gel column chromatography (eluent: 95/5 hexane/ethyl acetate) to afford 300 mg (0.81 mmol, yield: 99%) of **27a** as a clear yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 2.1 Hz, 1H), 7.07 (d, J = 2.1 Hz, 1H), 6.21 (tt, J = 55.2 Hz, J = 4.1 Hz, 1H), 4.08 (dt, J = 13.1 Hz, J = 4.0 Hz, 2H), 3.30 (m, 1H), 2.82 (m, 1H), 1.22 (d, J = 7.0 Hz, 12H).

3,5-Di-*iso*-propyl-6-(3-fluoropropoxy)iodobenzene (27b). Alkylation of 2.30 g (7.56 mmol) of **16** in the presence of 1.07 g (7.56 mmol) of 1-bromo-3-fluoropropane and 3.70 g (11.30 mmol) of Cs_2CO_2 according to the procedure described for the synthesis of **27a** affords 2.80 g (7.50 mmol, yield: 99%) of **27b** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 1.8 Hz, 1H), 7.06 (d, J = 2.0 Hz, 1H), 4.75 (dt, J = 47.3 Hz, J = 5.8 Hz, 2H), 3.95 (t, J = 5.9 Hz, 2H), 3.27 (m, 1H), 2.81 (m, 1H), 2.24 (dt, J = 26.0, 6.0 Hz, 2H), 1.22 (d, J = 7.0 Hz, 6H), 1.21 (d, J = 7.0 Hz, 6H).

3,5-Di-*iso*-propyl-6-(2,2,2-trifluoroethoxy) iodobenzene (27c). To a solution of 1.13 g (3.7 mmol) of **16** and 1.21 g (7.4 mmol) of 1-bromo-2,2,2-trifluoroethane in 15 mL of dry DMF in a 50 mL pressure tube was added 2.41 g (7.4 mmol) of Cs_2CO_3 at room temperature. The tube was sealed and the mixture was stirred overnight at 50 °C. After cooling the sample to room temperature, the tube was carefully open and water was added (30 mL). The solution was extracted with ethyl acetate (2 × 50 mL) and the organic layers were washed (with water and brine successively) and dried ($MgSO_4$). After concentration, the residue was purified over silica gel column chromatography (eluent: 97.5/2.5 hexane/ethyl acetate) to afford 1.29 g (33.6 mmol, yield: 91%) of **27c** as a clear colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 2.0 Hz, 1H), 7.08 (d, J = 2.0 Hz, 1H), 4.29 (d, J = 8.3 Hz, 1H), 4.25 (d, J =

8.4 Hz, 1H), 3.32 (heptet, J = 6.9 Hz, 1H), 2.83 (heptet, J = 6.9 Hz, 1H), 1.21 (d, J = 6.9 Hz, 12H).

3,5-Di-*tert*-butyl-6-(2,2-difluoroethoxy) iodobenzene (28a). Alkylation of 3.0 g (9.03 mmol) of **26** in the presence of 1.57 g (10.84 mmol) of 1-bromo-2,2-difluoroethane and 520 mg (10.84 mmol) of NaH according to the procedure described for the synthesis of **17** affords 3.29 g (8.31 mmol, yield: 92%) of **28a** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 2.4 Hz, 1H), 7.35 (d, J = 2.4 Hz, 1H), 6.28 (tt, J = 55.2, 4.3 Hz, 1H), 4.23 (td, J = 13.4, 4.3 Hz, 2H), 2.56 (dd, J = 15.2, 7.6 Hz, 2H), 1.39 (s, 9H), 1.29 (s, 9H).

3,5-Di-*tert*-butyl-6-(3-fluoropropoxy)iodobenzene (28b). Alkylation of 4.00 g (12.04 mol) of **26** in the presence of 2.03 g (14.48 mol) of 1-bromo-3-fluoropropane and 695 mg (14.48 mol) of NaH according to the procedure described for the synthesis of **17** affords 4.39 g (11.97 mol, yield: 93%) of **28b** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 2.4 Hz, 1H), 7.33 (d, J = 2.4 Hz, 1H), 4.80 (t, J = 6.0 Hz, 1H), 4.71 (t, J = 6.0 Hz, 1H), 4.11 (t, J = 6.1 Hz, 2H), 2.31 (m, 1H), 2.26 (m, 1H), 1.39 (s, 9H), 1.29 (s, 9H).

1-[3,5-Di-*iso*-propyl-6-(2,2-difluoroethoxy)benzene]-2-formylthiophene (29a). Reaction of 300 mg (0.82 mmol) of **27a** and 152 mg (0.98 mmol) of 2-formylthiophene-3-boronic acid in the presence of 94 mg (0.082 mmol, 5%) of $Pd(PPh_3)_4$ according to the procedure described for the synthesis of **19** affords 219 mg (0.62 mmol, yield: 76%) of the corresponding adduct **29a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.76 (d, J = 5.1 Hz, 1H), 7.26 (d, J = 5.0 Hz, 1H), 7.20 (d, J = 2.1 Hz, 1H), 7.02 (d, J = 2.2 Hz, 1H), 5.69 (tt, J = 55.2, 4.1 Hz, 1H), 3.59 (dd, J = 13.5, 4.0 Hz, 1H), 3.55 (dd, J = 13.5, 4.1 Hz, 1H), 3.37 (septet, J = 6.9 Hz, 1H), 2.92 (septet, J = 6.9 Hz, 1H), 1.27 (d, J = 6.9 Hz, 6H), 1.26 (d, J = 7.0 Hz, 6H).

1-[3,5-Di-*iso*-propyl-6-(3-fluoropropoxy)benzene]-2-formylthiophene (29b). Reaction of 200 mg (0.55 mmol) of **27b** and 103 mg (0.66 mmol) of 2-formylthiophene-3-boronic acid in the presence of 63.0 mg (0.055 mmol, 5%) of $Pd(PPh_3)_4$ according to the procedure described for the synthesis of **19** affords 159 mg (0.46 mmol, yield: 83%) of **29b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (d, J = 0.9 Hz, 1H), 7.74 (dd, J = 4.9 Hz, J = 0.8 Hz, 1H), 7.24 (d, J = 4.9 Hz, 1H), 7.18 (d, J = 2.2 Hz, 1H), 7.01 (d, J = 2.2 Hz, 1H), 4.43 (dt, J = 47.1, 5.9 Hz, 2H), 3.49 (t, J = 6.0 Hz, 2H), 3.32 (septet, J = 6.9 Hz, 1H), 2.91 (septet, J = 6.9 Hz, 1H), 1.82 (m, 2H), 1.27 (d, J = 6.9 Hz, 6H), 1.26 (d, J = 6.9 Hz, 6H).

1-[3,5-Di-*iso*-propyl-6-(2,2,2-trifluoroethoxy)benzene]-2-formylthiophene (29c). Reaction of 250.0 mg (0.65 mmol) of **27c** in the presence of 120.0 mg (0.71 mmol) of 2-formylthiophene-3-boronic acid and 75.0 mg (0.065 mmol) of $Pd(PPh_3)_4$ according to the procedure described for the synthesis of **19**, affords 102.0 mg (0.27 mmol, yield: 42.4%) of **29c** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (d, J = 1.0 Hz, 1H), 7.78 (dd, J = 4.9, 1.1 Hz, 1H), 7.28 (d, J = 4.9 Hz, 1H), 7.21 (d, J = 2.2 Hz, 1H), 7.02 (d, J = 2.2 Hz, 1H), 3.69 (dd, J = 16.7, 8.4 Hz, 2H), 3.38 (septet, J = 6.9 Hz, 1H), 2.92 (septet, J = 6.9 Hz, 1H), 1.27 (d, J = 7.0 Hz, 6H), 1.26 (d, J = 7.0 Hz, 6H).

Ethyl-(*2E*,*4E*,*6Z*)-[3-methyl-6,7-(2,3-thienyl)-7-[3,5-di-*iso*-propyl-6-(2,2-difluoroethoxy)benzene]pentane-2,4,6-trienoate (30a). Reaction of 219 mg (0.62 mmol) of **29a** in the presence of the anion of triethyl-3-methyl-phosphonocrotonate (generated from 0.45 mL, 1.9 mmol of of triethyl-3-methyl-phosphonocrotonate and 0.80 mL of *n*BuLi in hexanes 2.5 M in THF-DMPU 7.0 mL) according to the procedure described for the synthesis of **24a** affords 272 mg (0.59 mmol, yield: 94%) of the corresponding ester **30a** as a mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 5.2 Hz, 1H), 7.15 (d, J = 5.2 Hz, 1H), 7.12 (d, J = 2.1 Hz, 1H), 6.99 (d, J = 15.9 Hz, 1H), 6.93 (d, J = 2.1 Hz, 1H), 6.66 (d, J = 15.9 Hz, 1H), 5.86 (s, 1H), 5.68 (tt, J = 55.2, 3.8 Hz, 1H), 4.17 (q, J = 7.0 Hz, 2H), 3.56 (dt, J = 13.7, 4.2 Hz, 2H), 3.37 (m, 1H), 2.90 (m, 1H), 2.25 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H), 1.27 (d, J = 7.0 Hz, 6H), 1.26 (d, J = 7.0 Hz, 6H).

Ethyl-(*2E*,*4E*,*6Z*)-[3-methyl-6,7-(2,3-thienyl)-7-[3,5-di-*iso*-propyl-6-(3-fluoropropoxy)benzene]pentane-2,4,6-trienoate (30b). Reaction of 159 mg (0.46 mmol) of **29b** in the presence of the anion of triethyl-3-methyl-phosphonocrotonate (generated from 0.33 mL, 1.4 mmol of of triethyl-3-methyl-phosphonocrotonate and 0.6 mL of *n*BuLi in hexanes 2.5 M in THF-DMPU 5.0 mL) according to the procedure described for the synthesis of **24a** affords 200 mg (0.44 mmol, yield: 95%) of the corresponding ester **30b** as a mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 5.2 Hz, 1H), 7.14 (d, J = 4.9 Hz, 1H), 7.11 (d, J = 2.1 Hz, 1H), 7.02 (d, J = 15.9 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 6.64 (d, J = 15.9 Hz, 1H), 5.85 (s, 1H), 4.43 (dt, J = 47.0, 6.1 Hz, 2H), 4.17 (q, J = 7.0 Hz, 2H), 3.49 (t, J = 6.0 Hz, 2H), 3.32 (m, 1H), 2.89 (m, 1H), 2.25 (d, J = 1.2 Hz, 3H), 1.83 (dt, J = 24.7, 6.0 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H), 1.28 (d, J = 7.0 Hz, 6H), 1.25 (d, J = 6.8 Hz, 6H).

Ethyl-(*2E*,*4E*,*6Z*)-[3-methyl-6,7-(2,3-thienyl)-7-[3,5-di-*iso*-propyl-6-(2,2,2-trifluoroethoxy)benzene]pentane-2,4,6-trienoate (30c). Reaction of 102.0 mg (0.27 mmol) of **29c** in the presence of the anion of triethyl-3-methyl-phosphonocrotonate (generated from 0.20 mL, 0.83 mmol of triethyl-3-methyl-phosphonocrotonate and 0.35 mL of *n*-BuLi in hexanes 2.5 M in THF-DMPU 5.0 mL) according to the procedure described for the synthesis of **24a** affords 132.0 mg (0.27 mmol, yield: 100%) of the corresponding ester **30c** as a mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 5.2 Hz, 1H), 7.16 (d, J = 5.2 Hz,), 7.14 (d, J = 2.0 Hz, 1H), 7.00 (d, J = 15.8 Hz, 1H), 6.94 (d, J = 2.1 Hz, 1H), 6.68 (d, J = 15.8 Hz, 1H), 5.87 (s, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.67 (q, J = 8.5 Hz, 2H), 3.41 (m, 1H), 2.91 (m, 1H), 2.26 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.27 (d, J = 6.6 Hz, 6H), 1.25 (d, J = 6.7 Hz, 6H).

(*2E*,*4E*,*6Z*)-[3-Methyl-6,7-(2,3-thienyl)-7-[3,5-di-*iso*-propyl-6-(2,2-difluoropropoxy) benzene]pentane-2,4,6-trienoic acid (31a). Saponification of 272.0 mg (0.59 mmol) of **30a** in the presence of 0.90 mL of LiOH (2 M aqueous solution) in a 1/1 mixture of THF/MeOH (3.0/3.0 mL) according to the procedure described for the synthesis of **25a** affords 101.3 mg (0.25 mmol, yield: 42%) of the desired acid **31a** as a single stereoisomer (yellow solid, mp = 158.5−160.9 °C, CH_3CN). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 5.1 Hz, 1H), 7.16 (d, J = 5.0 Hz, 1H), 7.13 (d, J = 2.1 Hz, 1H), 7.05 (d, J = 15.8 Hz, 1H), 6.93 (d, J = 2.2 Hz, 1H), 6.69 (d, J = 15.8 Hz, 1H), 5.89 (s, 1H), 5.68 (tt, J = 55.4, 4.2 Hz, 1H) 3.56 (dt, J = 13.7, 4.1 Hz, 2H), 3.37 (m, 1H), 2.91 (m, 1H), 2.27 (s, 3H), 1.28 (d, J = 6.9 Hz, 6H), 1.26 (d, J = 7.1 Hz, 6H). Anal. ($C_{24}H_{28}F_2O_3S$) C, H, S. MS (EI, 70 eV) 434 *m/z* 434 (MH^+, 50), 416 (100), 374 (35). 334 (20). HRMS for $C_{24}H_{29}F_2O_3S$ (MH^+): calcd, 434.1727; found, 434.1854.

(*2E*,*4E*,*6Z*)-[3-Methyl-6,7-(2,3-thienyl)-7-[3,5-di*iso*-propyl-6-(3-fluoropropoxy) benzene]pentane-2,4,6-trienoic Acid (31b). Saponification of 200 mg (0.44 mmol) of **30b** in the presence of 0.7 mL of LiOH (2 M aqueous solution) in a 1/1 mixture of THF/MeOH (2.5/2.5 mL) according to the procedure described for the synthesis of **25a** affords 46.7 mg (0.11 mmol, yield: 25%) of the desired acid **31b** as a single stereoisomer (yellow solid, mp = 145.2−147.7 °C, CH_3CN). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 5.1 Hz, 1H), 7.14 (d, J = 5.0 Hz, 1H), 7.12 (d, J = 2.2 Hz, 1H), 7.07 (d, J = 15.8 Hz, 1H), 6.92 (d, J = 2.2 Hz, 1H), 6.67 (d, J = 15.8 Hz, 1H), 5.89 (s, 1H), 4.42 (dt, J = 47.1, 6.0 Hz, 2H), 3.49 (t, J = 6.0 Hz, 2H), 3.32 (m, 1H), 2.90 (m, 3H), 2.27 (s, 3H), 1.83 (dp, J = 6.0 Hz, 2H), 1.28 (d, J = 7.5 Hz, 6H), 1.26 (d, J = 7.5 Hz, 6H). Anal. ($C_{25}H_{31}FO_3S$); C: calcd, 69.74; found: 69.60; H: calcd, 7.26; found: 7.34; S: calcd, 7.45; found: 7.30. MS (EI, 70 eV) 430 *m/z* 430 (MH^+, 30), 412 (100), 370 (40). 330 (25). HRMS Calcd for $C_{25}H_{32}FO_3S$: 430.1978. Found: 430.2072.

(*2E*,*4E*,*6Z*)-[3-Methyl-6,7-(2,3-thienyl)-7-[3,5-di-*iso*-propyl-6-(2,2,2-trifluoroethoxy) benzene]pentane-2,4,6-trienoic Acid (31c). Saponification of 132.0 mg (0.27 mmol) of **30c** in the presence of 0.41 mL of LiOH (2 M aqueous solution) in a 1/1 mixture of THF/MeOH (2.0/2.0 mL) according to the procedure described for the synthesis of **25a** affords 24.9 mg (0.054 mmol, yield: 20%) of the desired acid **31c** as a single stereoisomer (pale yellow solid, mp = 149−151.5 °C, CH_3CN). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 5.1 Hz, 1H), 7.17 (d,

J = 5.0 Hz,), 7.14 (d, J = 2.0 Hz, 1H), 7.05 (d, J = 15.8 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 6.70 (d, J = 15.8 Hz, 1H), 5.89 (s, 1H), 3.67 (q, J = 8.5 Hz, 2H), 3.41 (m, 1H), 2.91 (m, 1H), 2.27 (s, 3H), 1.27 (d, J = 6.4 Hz, 6H), 1.26 (d, J = 6.6 Hz, 6H). Anal. ($C_{24}H_{27}F_3O_3S$) C, H, S. MS (EI, 70 eV) 452 *m*/*z* 452 (MH^+, 100), 434 (90), 392 (30), 352 (40). HRMS for $C_{24}H_{28}F_3O_3S$ (MH^+); calcd, 452.1663, found: 452.1770.

2-[3,5-Di-*iso*-propyl-6-(3-fluoropropoxy)benzene]-3-formylfuran (32). Reaction of 1.05 g (2.88 mmol) of **27b** and 610 mg (4.30 mmol) of 3-formylfuran-2-boronic acid in the presence of 166 mg (0.14 mmol, 5%) of $Pd(PPh_3)_4$ and 2.9 mL of a 2 N Na_2CO_2 aqueous solution in refluxing DME (25 mL) afford after workup and silica gel column chromatography (eluent: 95/5 and 90/10 hexane/ethyl acetate) 108 mg (0.32 mmol, yield: 11%) of the corresponding adduct **32**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 7.52 (d, J = 1.9 Hz, 1H), 7.25 (d, J = 2.2 Hz, 1H), 7.17 (d, J = 2.2 Hz, 1H), 6.89 (d, J = 1.9 Hz, 1H), 4.56 (t, J = 5.7 Hz, 1H), 4.45 (t, J = 5.7 Hz, 1H), 3.63 (t, J = 6.1 Hz, 2H), 3.32 (m, 1H), 2.92 (m, 1H), 1.95 (m, 1H), 1.88 (m, 1H), 1.27 (d, J = 6.9 Hz, 12H).

Ethyl-(*2E*,*4E*,*6Z*)-3-methyl-6,7-(3,4-furyl)-7-[3,5-di-*iso*-propyl-6-(3-fluoropropoxybenzene]pentane-2,4,6-trienoate (33). Reaction of 108 mg (0.32 mmol) of **32** in the presence of the anion of triethyl-3-methyl-phosphonocrotonate (generated from 0.20 mL (0.81 mmol) of of triethyl-3-methyl-phosphonocrotonate and 0.6 mL of *n*BuLi in hexanes 1.6 M in THF-DMPU 5/0.5 mL) according to the procedure described for the synthesis of **24a** affords 140 mg (0.31 mmol, yield: 97%) of the corresponding ester **33** as a mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 1.7 Hz, 1H), 7.16 (d, J = 2.2 Hz, 1H), 7.09 (d, J = 2.2 Hz, 1H), 6.94 (d, J = 15.9 Hz, 1H), 6.70 (d, J = 2.0 Hz, 1H), 6.54 (d, J = 15.9 Hz, 1H), 5.83 (s, 1H), 4.57 (t, J = 5.8 Hz, 1H), 4.45 (t, J = 5.8 Hz 1H), 4.17 (dd, J = 14.5, 7.3 Hz, 2H), 3.62 (t, J = 6.0 Hz, 2H), 3.34(m, 1H), 2.93 (m, 1H), 2.29 (s, 3H), 1.95 (m, 1H), 1.81 (m, 1H), 1.43 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H), 1.26 (t, J = 7.2 Hz, 12H).

(*2E*,*4E*,*6Z*)-3-Methyl-6,7-(3,4-furyl)-7-[3,5-di-*iso*-propyl-6-(3-fluoropropoxybenzene] pentane-2,4,6-trienoic Acid (34). Saponification of 130 mg (0.29 mmol) of **33** in the presence of 1.5 mL of LiOH (2 M aqueous solution) in a 1/1 mixture of THF/MeOH (5/5 mL) according to the procedure described for the synthesis of **25a** affords 87 mg (0.23 mmol, yield: 77%) of the desired acid **34** as a single stereoisomer (yellow solid, mp 138 °C CH_3CN). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 1.9 Hz, 1H), 7.17 (d, J = 2.3 Hz, 1H), 7.09 (d, J = 2.3 Hz, 1H), 6.99 (d, J = 15.9 Hz, 1H), 6.72 (d, J = 1.9 Hz, 1H), 6.57 (d J = 15.9 Hz, 1H), 5.86 (s, 1H), 4.57 (t, J = 5.9 Hz, 1H), 4.45 (t, J = 5.8 Hz, 1H), 3.63 (t, J = 6.0 Hz, 2H), 3.34 (dt, J = 13.9, 6.9 Hz, 1H), 2.91 (dt, J = 13.9, 6.9 Hz, 1H), 2.31 (s, 3H), 1.95 (m, 1H), 1.90 (m, 1H), 1.27 (d, J = 6.9 Hz, 6H), 1.26 (d, J = 6.9 Hz, 6H). Anal. ($C_{25}H_{31}FO_4$) C, H. MS (EI, 70 eV) 415 *m*/*z* 415 (MH^+, 15), 397 (80), 375 (95), 357 (45), 293 (100), 275 (55). HRMS for $C_{25}H_{32}FO_4$ (MH^+); calcd, 415.2282, found: 415.2301.

1-[3,5-Di-*iso*-propyl-6-(2,2-difluoroethoxy)benzene]-2-formylbenzene (35a). Reaction of 1.93 g (5.3 mmol) of **27a** and 0.87 g (5.8 mmol) of 2-carboxybenzeneboronic acid in the presence of 303 mg (0.26 mmol, 5%) of $Pd(PPh_3)_4$ according to the procedure described for the synthesis of **19** affords 1.48 g (4.3 mmol, yield: 81%) of the corresponding adduct **35a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.05 (d, J = 7.6 Hz, 1H), 7.68 (dd, J = 7.6, 7.4 Hz, 1H), 7.53 (dd, J = 7.6, 7.4 Hz, 1H), 7.46 (d, J = 7.4 Hz, 1H), 7.20 (d, J = 2.3 Hz, 1H), 7.01 (d, J = 2.3 Hz, 1H), 5.53 (tt, J = 55, 4.2 Hz, 1H), 3.55 (m, 1H), 3.34 (m, 2H), 2.93 (septet, J = 6.9 Hz, 1H), 1.67 (m, 2H), 1.28 (d, J = 6.9 Hz, 6H), 1.27 (d, J = 6.9 Hz, 6H).

1-[3,5-Di-*iso*-propyl-6-(3-fluoropropoxy)benzene]-2-formylbenzene (35b). Reaction of 2.15 g (5.9 mmol) of **27b** and 0.975 g (6.5 mmol) of 2-carboxybenzeneboronic acid in the presence of 341 mg (0.29 mmol, 5%) of $Pd(PPh_3)_4$ according to the procedure described for the synthesis of **19** affords 1.544 g (4.5 mmol, yield: 76%) of the corresponding adduct **35b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.02 (d, J = 7.6 Hz, 1H), 7.66 (dd, J = 7.6, 7.4 Hz, 1H), 7.50 (dd, J = 7.6, 7.4 Hz, 1H), 7.46 (d, J = 7.4 Hz, 1H), 7.18 (d, J = 2.2 Hz, 1H), 7.02 (d, J = 2.2 Hz, 1H), 4.46−4.10 (m, 2H), 3.52 (m, 1H), 3.30 (septet, J = 6.9 Hz, 1H), 3.24 (m, 1H), 2.93 (septet, J = 6.9 Hz, 1H), 1.67 (m, 2H), 1.28 (d, J = 6.9 Hz, 6H), 1.27 (d, J = 6.9 Hz, 6H).

1-[3,5-di-*tert*-butyl-6-(3-fluoropropoxy)benzene]-2-formylbenzene (36). Reaction of 1.83 g (5.3 mmol) of **28b** and 874 mg (5.8 mmol) of 2-formylbenzeneboronic acid in the presence of 306 mg (0.2 mmol, 4%) of $Pd(PPh_3)_4$ according to the procedure described for the synthesis of **19** affords 512 mg (1.4 mmol, yield: 27%) of the corresponding adduct **36**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (s, 1H), 8.03 (dd, J = 8.0, 1.5 Hz, 1H), 7.69 (ddd, J = 8.0, 7.0, 1.5 Hz, 1H), 7.52−7.48 (m, 2H), 7.42(d, J = 2.4 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 4.35 (dddd, J = 47, 9.2, 6.7, 5.4 Hz, 1H), 4.19 (dddd, J = 47, 9.2, 6.0, 5.9 Hz, 1H), 3.55(ddd, J = 9.1, 6.1, 5.9 Hz, 1H), 3.23 (ddd, J = 9.2, 6.1, 5.9 Hz, 1H), 1.65 (m, 2H), 1.42 (s, 9H), 1.34 (s, 9H).

Ethyl-(*2E*,*4E*,*6Z*)-3-methyl-6,7-cyclohexanedienyl-7-[3,5-di*iso*-propyl-6-(2,2-difluoroethoxybenzene] pentane-2,4,6-trienoate (37a). Reaction of 1.48 g (4.3 mmol) of **35a** in the presence of the anion of triethyl-3-methyl-phosphonocrotonate (generated from 3.21 g, 12.2 mmol, of triethyl-3-methyl-phosphonocrotonate and 5.0 mL of *n*-BuLi in hexanes 2.5 M in THF-DMPU 20/10 mL) according to the procedure described for the synthesis of **24a** affords 1.80 g (4.0 mmol, yield: 93%) of the corresponding ester **37a** as a mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, 1H, J = 7.4 Hz, 1H), 7.41−7.35 (m, 3H), 7.13 (d, J = 2.1 Hz, 1H), 6.89 (d, J = 2.1 Hz, 1H),), 6.83 (d, J = 16 Hz, 1H), 6.74 (d, J = 16 Hz, 1H), 5.86 (s, 1H), 5.47 (tt, J = 55, 4.2 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.53−3.40 (m, 2H), 3.35 (septet, J = 6.9 Hz, 1H), 2.90 (septet, J = 6.9 Hz, 1H), 2.17 (s, 3H), 1.33−1.20 (m, 15H).

Ethyl-(*2E*,*4E*,*6Z*)-3-methyl-6,7-cyclohexanedienyl-7-[3,5-di*iso*-propyl-6-(3-fluoropropoxybenzene] pentane-2,4,6-trienoate (37b). Reaction of 1.54 g (4.5 mmol) of **35b** in the presence of the anion of triethyl-3-methyl-phosphonocrotonate (generated from 3.575 g, 13.5 mmol, of triethyl-3-methyl-phosphonocrotonate and 5.4 mL of *n*BuLi in hexanes 2.5 M in THF-DMPU 20/10 mL) according to the procedure described for the synthesis of **24a** affords 1.90 g (4.2 mmol, yield: 93%) of the corresponding ester **37b** as a mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, 1H, J = 7.2 Hz, 1H), 7.40−7.35 (m, 3H), 7.12 (d, J = 1.9 Hz, 1H), 6.87 (d, J = 1.9 Hz, 1H), 6.85 (d, J = 16 Hz, 1H), 6.73 (d, J = 16 Hz, 1H), 5.85 (s, 1H), 4.27 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 3.47−3.39 (m, 2H), 3.30 (septet, J = 6.9 Hz, 1H), 2.89 (septet, J = 6.9 Hz, 1H), 2.17 (s, 3H), 1.69 (m, 2H), 1.25 (m, 15H).

Ethyl-3-[3,5-di-*iso*-propyl-6-(3-fluoropropoxybenzene]-4-[(*2E*,*4E*)-3-methyl-pentadiene-2,4-dienoate]benzene (38). Reaction of 521 mg (1.4 mmol) of **36** in the presence of the anion of triethyl-3-methyl-phosphonocrotonate (generated from 1.1 g, 4.2 mmol, of triethyl-3-methyl-phosphonocrotonate and 1.6 mL of *n*-BuLi in hexanes 2.5 M in THF-DMPU 15/5 mL) according to the procedure described for the synthesis of **24a** affords 279 mg (0.58 mmol, yield: 41%) of the corresponding ester **38** as a mixture of isomers.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (m, 1H), 7.36 (m, 4H), 7.02 (d, J = 2.4 Hz, 1H), 6.88 (d, J = 16 Hz, 1H), 6.76 (d, J = 16 Hz, 1H), 5.86 (s, 1H), 4.25 (m, 2H), 4.17(q, J = 7.0 Hz, 2H), 3.44 (m, 2H), 2.18 (d, J = 0.9 Hz, 3H), 1.68 (m, 2H), 1.39 (s, 9H), 1.31 (s, 9H), 1.30 (t, J = 7.0 Hz, 3H).

(*2E*,*4E*,*6Z*)-3-Methyl-6,7-cyclohexanedienyl-7-[3,5-di*iso*-propyl-6-(2,2-difluoroethoxybenzene]pentane-2,4,6-trienoic Acid (39a). Saponification of 1.80 g (4.0 mmol) of **37a** in the presence of 0.50 g of LiOH−H_2O (11.9 mmol) in a 2/2/1 mixture of THF/EtOH/H_2O (20/20/10 mL) according to the procedure described for the synthesis of **25a** affords 1.049 g (2.45 mmol, yield: 62%) of the desired acid **39a** as a single stereoisomer (pale yellow solid, mp 157−159 °C, CH_3CN). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, J = 7.2, 2.3 Hz, 1H), 7.43−7.35 (m, 3H), 7.14 (d, J = 2.2 Hz, 1H), 6.89 (d, J = 2.2 Hz, 1H), 6.88 (d, J = 16 Hz, 1H), 6.76 (d, J = 16 Hz, 1H), 5.88 (s, 1H), 5.48 (tt, J = 55.5, 4.2 Hz, 1H), 3.48 (dtd, J = 27, 12.8, 4.2

Hz, 2H), 3.35 (septet, J = 6.9 Hz, 1H), 2.90 (septet, J = 6.9 Hz, 1H), 2.18 (s, 3H), 1.25 (d, J = 6.9 Hz, 12H). Anal. ($C_{26}H_{30}F_2O_3$) C, H. MS (EI, 70 eV) 428 *m/z* 428 (MH^+, 25), 410 (60), 368 (100), 328 (85), 286 (75). HRMS for $C_{26}H_{31}F_2O_3$ (MH^+); calcd, 428.2163, found, 428.2249.

(*2E,4E,6Z*)-3-Methyl-6,7-cyclohexanedienyl-7-[3,5-di-*iso*-propyl-6-(3-fluoropropoxy benzene]pentane-2,4,6-trienoic Acid (39b). Saponification of 1.90 g (4.2 mmol) of **37b** in the presence of 0.88 g of $LiOH-H_2O$ (21.0 mmol) in a 2/2/1 mixture of THF/MeOH/H_2O (50 mL) according to the procedure described for the synthesis of **25a** affords 1.02 g (2.4 mmol, yield: 57%) of the desired acid **39b** as a single stereoisomer (white solid, mp 161−163 °C, CH_3CN). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, 1H, J = 7.5 Hz, 1H), 7.40−7.35 (m, 3H), 7.12 (d, J = 2.1 Hz, 1H), 6.91 (d, J = 16 Hz, 1H), 6.87 (d, J = 2.1 Hz, 1H), 6.76 (d, J = 16 Hz, 1H), 5.87 (s, 1H), 4.29 (dt, J = 17.9, 6.1 Hz, 1H), 4.18 (dt, J = 17.9, 6.1 Hz, 1H), 3.45 (t, J = 6.0 Hz, 1H), 3.40 (t, J = 6.0 Hz, 1H), 3.30 (septet, J = 6.9 Hz, 1H), 2.89 (septet, J = 6.9 Hz, 1H), 2.18 (s, 3H), 1.69 (m, 2H), 1.25 (d, J = 6.9 Hz, 12H). Anal. ($C_{27}H_{33}FO_3$) C, H. MS (EI, 70 eV) 424 *m/z* 424 (MH^+, 15), 406 (70), 364 (100), 322 (40), 282 (40). HRMS Calcd $C_{27}H_{34}FO_3$ (MH^+); calcd, 424.2414, found, 424.2471.

3-[3,5-Di-*tert*-butyl-6-(3-fluoropropoxybenzene]-4-[(*2E,4E*)-3-methyl-pentadiene-2,4-dienoic acid]benzene (40). Saponification of 279 mg (0.58 mmol) of **38** in the presence of 243 mg of LiOH (5.8 mmol) in a 2/2/1 mixture of THF/EtOH/H_2O (6/6/3 mL) according to the procedure described for the synthesis of **25a** affords 260 mg (0.57 mmol, yield: 99%) of the desired acid **40** as a single stereoisomer (white solid, mp 177−178 °C, CH_3CN). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (m, 1H), 7.38 (m, 4H), 7.02 (d, J = 2.4 Hz, 1H), 6.93 (d, J = 15.9 Hz, 1H), 6.78 (d, J = 15.9 Hz, 1H), 5.89 (s, 1H), 4.26 (m, 2H), 3.44 (m, 2H), 2.19 (d, J = 0.7 Hz, 3H), 1.68 (m, 2H), 1.43 (s, 9H), 1.31 (s, 9H). Anal. ($C_{29}H_{37}FO_3$) C, H. MS (EI, 70 eV) 452 *m/z* 452 (MH^+, 15), 396 (30), 378 (100), 322 (55). HRMS for $C_{29}H_{38}FO_3$ (MH^+); calcd, 452.2727, found, 452.2786.

Synthesis of 3,5-Di-*iso*-propyl-6-(2,2,2-trifluoroethoxy)-benzene Boronic Acid (41). To a flame-dried 300 mL round-bottomed flask was charged with 100 mL of anhydrous Et_2O, **27c** (3.86 g, 10.0 mmol) and TMEDA (2.3 mL, 15.0 mmol). The resulting solution was cooled to −78 °C using a dry ice/acetone bath and 6.0 mL of *n*-BuLi solution (2.5 M in hexanes) was added dropwise via a syringe. The mixture was kept at −78 °C for 15 min and 3.4 mL of $B(OMe)_3$ (30.0 mmol) was added slowly. This resulting mixture was stirred at −78 °C for 1 h, slowly warmed to 0 °C. The reaction mixture was quenched with 50 mL of 1.0 M aqueous HCl solution and stirred at 23 °C for 1 h. The reaction mixture was extracted with EtOAc (2 × 150 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 5 × 20 cm, 15% EtOAc/hexane as eluent) to give desired boronic acid **41** 1.38 g (46%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 2.1 Hz, 1H), 7.26 (d, J = 2.1 Hz, 1H), 5.62 (s, 2H), 4.16 (q, J = 8.2 Hz, 2H), 3.25 (septet, J = 6.9 Hz, 1H), 2.91 (septet, J = 6.9 Hz, 1H), 1.26 (d, J = 6.9 Hz, 6H), 1.25 (d, J = 6.9 Hz, 6H).

2-[3,5-Di-*iso*-propyl-6-(2,2,2-trifluoroethoxy)benzene]-4-formylpyridine (42). Reaction of 174.1 mg (0.57 mmol) of **41** and 106.5 mg (0.57 mmol) of 3-bromo-4-carboxypyridine in the presence of 33 mg (0.029 mmol, 5%) of $Pd(PPh_3)_4$ according to the procedure described for the synthesis of **19** affords 150 mg (0.41 mmol, yield: 72%) of the corresponding adduct **42**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 8.85 (d, J = 4.9 Hz, 1H), 8.81(s, 1H), 7.82 (d, J = 4.9 Hz, 1H), 7.27 (d, J = 2.2 Hz, 1H), 7.07 (d, J = 2.2 Hz, 1H), 3.74 (m, 1H), 3.47 (m, 1H), 3.33 (septet, J = 6.9 Hz, 1H), 2.97 (septet, J = 6.9 Hz, 1H), 1.29 (d, J = 6.9 Hz, 12H).

Ethyl-3-[3,5-di-*iso*-propyl-6-(2,2,2-trifluoroethoxybenzene]-4-[(*2E,4E*)-3-methyl-pentadiene-2,4-dienoate]pyridine (43). Reaction of 1.011 g (2.77 mmol) of **42** in the presence of the anion of triethyl-3-methyl-phosphonocrotonate (generated from 2.194 g, 8.30 mmol, of of triethyl-3-methyl-phosphonocrotonate and 3.4 mL of *n*-BuLi in hexanes 2.5 M in THF-DMPU 15/15 mL) according to the procedure described for the synthesis of **24a** affords 1.0876 g (2.28 mmol, yield: 83%) of the corresponding ester **43** as a mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.59 (d, J = 5.3 Hz, 1H), 7.54 (d, J = 5.3 Hz, 1H), 7.20 (d, J = 2.1 Hz, 1H), 6.92 (d, J = 2.1 Hz, 1H), 6.89 (d, J = 16 Hz, 1H), 6.74 (d, J = 16 Hz, 1H), 5.93 (s, 1H), 4.18 (q, J = 7.0 Hz, 2H), 3.65 (m, 1H), 3.56 (m, 1H), 3.35 (septet, J = 6.9 Hz, 1H), 2.93 (septet, J = 6.9 Hz, 1H), 2.19 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H), 1.27 (d, J = 6.9 Hz, 6H), 1.26 (d, J = 6.9 Hz, 6H).

3-[3,5-Di-*iso*-propyl-6-(2,2,2-trifluoroethoxybenzene]-4-[(*2E,4E*)-3-methyl-pentadiene-2,4-dienoic acid]pyridine (44). Saponification of 1.0876 g (2.28 mmol) of **43** in the presence of 0.4798 g of LiOH (11.4 mmol) in a 2/2/1 mixture of THF/EtOH/H_2O (12/12/6 mL) according to the procedure described for the synthesis of **25a** affords 665.2 mg (1.49 mmol, yield: 65%) of the desired acid **44** as a single stereoisomer (white solid, mp 262−263 °C, CH_3CN). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.61 (d, J = 5.3 Hz, 1H), 7.56 (d, J = 5.3 Hz, 1H), 7.21 (d, J = 2.1 Hz, 1H), 6.93 (d, J = 2.1 Hz, 1H), 6.92 (d, J = 16 Hz, 1H), 6.79 (d, J = 16 Hz, 1H), 5.97 (s, 1H), 3.67 (m, 1H), 3.56 (m, 1H), 3.35 (septet, J = 6.9 Hz, 1H), 2.93 (septet, J = 6.9 Hz, 1H), 2.21 (s, 3H), 1.27 (d, J = 6.9 Hz, 12H). Anal. ($C_{25}H_{28}F_3NO_3$) C, H, N. MS (EI, 70 eV) 447 *m/z* 447 (MH^+, 100), 447 (100). HRMS for $C_{25}H_{29}F_3NO_3$ (MH^+); calcd, 447.2021, found, 447.2178.

Ethyl-2-[3,5-di-*iso*-propyl-6-(2,2,2-trifluoroethoxy)benzene]cyclopentene-1-carboxylate (45). Reaction of 200.0 mg (0.66 mmol) of **41** in the presence of 208.0 mg (0.16 mL, 0.72 mmol) of triflate and 76.0 mg (0.066 mmol) of $Pd(PPh_3)_4$ according to the procedure described for the synthesis of **19**, affords 258.0 mg (0.65 mmol, yield: 98%) of **45** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 1.9 Hz, 1H), 6.74 (d, J = 1.9 Hz, 1H), 4.10 (d, J = 8.6 Hz, 1H), 4.05 (d, J = 8.6 Hz, 1H), 3.99 (q, J = 7.1 Hz, 2H), 3.32 (septet, J = 6.9 Hz, 1H), 2.83 (m, 5H), 2.01 (m, 4H), 1.23 (d, J = 7.0 Hz, 6H), 1.21 (d, J = 7.0 Hz, 6H), 0.98 (t, J = 7.1 Hz, 3H).

1-[3,5-di-*iso*-propyl-6-(2,2,2-trifluoroethoxy)benzene] cyclopentene-2-methanol (46). To 0.258 g (0.65 mmol) of **45** dissolved in 10 mL of anhydrous diethyl ether in a flame dried 25 mL round-bottom flask at 0 °C was added 0.030 g (0.78 mmol) of $LiAlH_4$ portion-wise. The resultant mixture is stirred for 1.0 h at 0 °C. After such time, water (0.014 mL, 0.78 mmol) was added, followed by 6 N aqueous sodium hydroxide (0.26 mL, 1.55 mmol). The resultant mixture was allowed to warm to ambient temperature, stirred for 0.5 h, filtered through a plug of silica gel (eluting with diethyl ether) and concentrated under reduced pressure to give 0.225 g (0.63 mmol, yield: 97%) of alcohol **46** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, J = 2.2 Hz, 1H), 6.80 (d, J = 2.2 Hz, 1H), 4.09 (s, 2H), 4.00 (d, J = 8.5 Hz, 1H), 3.97 (d, J = 8.5 Hz, 1H), 3.33 (heptet, J = 6.9 Hz, 1H), 2.85 (heptet, J = 6.9 Hz, 1H), 2.74 (t, J = 7.2 Hz, 2H), 2.65 (t, J = 7.4 Hz, 2H), 2.01 (m, 2H), 1.52 (broad s, 1H), 1.23 (d, J = 6.8 Hz, 6H), 1.22 (d, J = 7.1 Hz, 6H).

1-[3,5-Di-*iso*-propyl-6-(2,2,2-trifluoroethoxy)benzene]-2-formylcyclopentene (47). 47 was synthesized from 0.225 g (0.66 mmol) of **46** and 0.11 g (0.95 mmol) NMO in the presence of 0.011 g (0.031 mmol) of TPAP according to the procedure described for the synthesis of **23a**. 0.222 g (0.63 mmol, yield: 95%) of **47** was isolated as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.14 (d, J = 2.2 Hz, 1H), 6.88 (d, J = 2.1 Hz, 1H), 3.99 (d, J = 8.4 Hz, 1H), 3.96 (d, J = 8.3 Hz, 1H), 3.31 (heptet, J = 6.9 Hz, 1H), 2.98 (m, 2H), 2.88 (heptet, J = 6.9 Hz, 1H), 2.73 (t, J = 7.6 Hz, 2H), 2.04 (m, 2H), 1.25 (d, J = 6.5 Hz, 6H), 1.23 (d, J = 6.7 Hz, 6H).

Ethyl-(*2E,4E,6Z*)-3-methyl-6,7-cyclopentenyl-7-[3,5-di-*iso*-propyl-6-(2,2,2-trifluoro ethoxybenzene]pentane-2,4,6-trienoate (48). Reaction of 222.0 mg (0.63 mmol) of **47** in the presence of the anion of triethyl-3-methyl-phosphonocrotonate (generated from 0.46 mL, 1.9 mmol of triethyl-3-methyl-phosphonocrotonate and 0.81 mL of *n*-BuLi in hexanes 2.5 M in THF-DMPU 8.0 mL) according to the procedure described

for the synthesis of **24a** affords 293 mg (0.63 mmol, yield: 100%) of the corresponding ester **48** as a mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, J = 2.1 Hz, 1H), 6.82 (d, J = 2.2 Hz, 1H), 6.79 (d, J = 15.8 Hz, 1H), 6.26 (d, J = 15.8 Hz, 1H), 5.81 (s, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.94 (q, J = 8.5 Hz, 2H), 3.35 (heptet, J = 6.9 Hz, 1H), 2.87 (m, 3H), 2.68 (t, J = 7.4 Hz, 2H), 2.21 (s, 3H), 2.03 (p, J = 7.4 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.25 (d, J = 6.9 Hz, 6H), 1.24 (d, J = 7.0 Hz, 6H).

(2*E*,4*E*,6*Z*)-3-Methyl-6,7-cyclopentenyl-7-[3,5-di-*iso*-propyl-6-(2,2,2-difluoroethoxy benzene]pentane-2,4,6-trienoic Acid (49). Saponification of 293 mg (0.63 mmol) of **48** in the presence of 0.94 mL of LiOH (2M aqueous solution) in a 1/1 mixture of THF/MeOH (4.0/4.0 mL) according to the procedure described for the synthesis of **25a** affords 76.3 mg (0.18 mmol, yield: 28%) of the desired acid **49** as a single stereoisomer (yellow solid, mp = 159.9−163.0 °C, CH_3CN). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 2.1 Hz, 1H), 6.83 (d, J = 15.7 Hz, 1H), 6.81 (d, J = 2.2 Hz, 1H), 6.28 (d, J = 15.7 Hz, 1H), 5.84 (s, 1H), 3.94 (q, J = 8.5 Hz, 2H), 3.35 (heptet, J = 6.9 Hz, 1H), 2.87 (m, 3H), 2.69 (t, J = 7.3 Hz, 2H), 2.22 (s, 3H), 2.04 (p, J = 7.4 Hz, 2H), 1.25 (d, J = 6.5 Hz, 6H), 1.23 (d, J = 6.4 Hz, 6H). Anal. ($C_{25}H_{31}F_3O_3$) C, H. MS (EI, 70 eV) 436 m/z 436 (MH^+, 100), 418 (50), 390 (80), 376 (30), 438 (30). HRMS for $C_{25}H_{32}F_3O_3$ (MH^+); calcd, 436.2225, found, 436.2281.

2-*tert*-Butyl-4-ethyl-6-iodophenol (51). Iodination of 50.0 g (0.30 mol) of 2-*tert*-butyl-4-methylphenol **50** in the presence of 74.2 g (0.33 mol) of NIS and 5.7 g (0.03 mol) of *p*-toluenesulfonic acid acid using the procedure described for the synthesis of **16** affords 88.2 g (0.29 mol, yield: 97%) of 2-*tert*butyl-4-ethyl-6-iodophenol **51** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 1.8 Hz, 1H), 7.06 (d, J = 1.9 Hz, 1H), 5.33 (s, 1H), 2.53 (dd, J = 15.2, 7.6 Hz, 2H), 1.38 (s, 9H), 1.19 (t, J = 7.6 Hz, 3H).

2-(2,2-Difluoroethoxy)-3-*tert*-butyl-5-ethylbenzene (52a). Alkylation of 478 mg (1.57 mmol) **51** with 273 mg (1.88 mmol) of 1-bromo-2,2-difluoroethane in the presence of 765 mg (2.35 mmol of Cs_2CO_3 in 3 mL of dry DMF according to the procedure described for the synthesis of **27a** affords 552 mg (1.50 mmol, yield: 97%) of **52a** as a clear yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 1.9 Hz, 1H), 7.14 (d, J = 1.9 Hz, 1H), 6.27 (tt, J = 55.5, 4.3 Hz, 1H), 4.23 (td, J = 13.2, 4.3 Hz, 2H), 2.56 (dd, J = 15.2, 7.6 Hz, 2H), 1.39 (s, 9H), 1.21 (t, J = 7.4 Hz, 3H).

2-(3-Fluoropropoxy)-3-*tert*-butyl-5-ethylbenzene (52b). Alkylation of 417 mg (1.37 mmol) **51** with 289 mg (2.06 mmol, 0.19 mL) of 1-bromo-3-fluoropropane in the presence of 669 mg (2.06 mmol of Cs_2CO_3 in 3 mL of dry DMF according to the procedure described for the synthesis of **27a** affords 489 mg (1.34 mmol, yield: 98%) of **52b** as a clear yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 1.8 Hz, 1H), 7.12 (d, J = 1.8 Hz, 1H), 4.80 (t, J = 5.9 Hz, 1H), 4.68 (t, J = 5.9 Hz, 1H), 4.09 (t, J = 6.4 Hz, 2H), 2.54 (dd, J = 15.2, 7.6 Hz, 2H), 2.26 (m, 1H), 2.23 (m, 1H), 1.37 (s, 9H), 1.20 (t, J = 7.6 Hz, 3H).

1-[3-Ethyl-5-*tert*-butyl-6-(2,2-difluoroethoxy)benzene]-2-formylthiophene (53a). Reaction of 261 mg (0.71 mmol) of **52a** and 165 mg (1.06 mmol) of 2-formylthiophene-3-boronic acid in the presence of 41 mg (0.035 mmol, 5%) of $Pd(PPh_3)_4$ according to the procedure described for the synthesis of **19** affords 243 mg (0.69 mmol, yield: 97%) of the corresponding adduct **53a**. 1H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.79 (d, J = 4.9 Hz, 1H), 7.27 (d, J = 4.9 Hz, 1H), 7.26 (d, J = 2.2 Hz, 1H), 7.02 (d, J = 2.2 Hz, 1H), 5.67 (tt, J = 55.0, 4.1 Hz, 1H), 3.58 (td, J = 13.4, 4.1 Hz, 2H), 2.65 (dd, J = 15.2, 7.6 Hz, 2H), 2.24 (s, 3H), 1.42 (s, 9H), 1.25 (t, J = 7.6 Hz, 3H).

1-[3-Ethyl-5-*tert*-butyl-6-(3-fluoropropoxy)benzene]-2-formylthiophene (53b). Reaction of 213 mg (0.58 mmol) of **52b** and 137 mg (0.88 mmol) of 2-formylthiophen-3-boronic acid in the presence of 34 mg (0.03 mmol, 5%) of $Pd(PPh_3)_4$ according to the procedure described for the synthesis of **19** affords 161 mg (0.46 mmol, yield: 79%) of the corresponding adduct **53b**. 1H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.77 (d, J = 5.2 Hz, 1H), 7.28 (d, J = 5.2 Hz, 1H), 7.27 (d, J = 2.1 Hz, 1H), 7.00 (d, J = 2.1 Hz, 1H), 4.45 (t, J = 5.9 Hz, 1H), 4.34 (t, J = 5.9 Hz, 1H), 3.50 (m, 2H), 2.64 (dd, J = 15.2, 7.6 Hz, 2H), 1.84 (m, 1H), 1.78 (m, 1H), 1.42 (s, 9H), 1.26 (t, J = 7.7 Hz, 3H).

Ethyl-(2*E*,4*E*,6*Z*)-3-methyl-6,7-(2,3-thienyk)-7-[3-ethyl-5-*tert*-butyl-6-(2,2-difluoro ethoxybenzene] pentane-2,4,6-trienoate (54a). Reaction of 243 mg (0.69 mmol) of **53a** in the presence of the anion of triethyl-3-methyl-phosphonocrotonate (generated from 0.62 mL, 2.5 mmol of of triethyl-3-methyl-phosphonocrotonate and 1.0 mL of *n*-BuLi in hexanes 2.5 M in THF-DMPU 5/0.5 mL) according to the procedure described for the synthesis of **24a** affords 190 mg (0.41 mmol, yield: 60%) of the corresponding ester **54a** as a mixture of isomers. 1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 5.2 Hz, 1H), 7.19 (d, J = 2.2 Hz, 1H), 7.10 (d, J = 5.2 Hz, 1H), 6.95 (d, J = 2.2 Hz, 1H), 6.94 (d, J = 15.8 Hz, 1 Hz, 2H), 5.86 (s, 1H), 5.63 (tt, J = 55.4, 4.1 Hz, 1H), 4.17 (dd, J = 14.2, 7.1 Hz, 2H), 3.59 (td, J = 13.5, 4.2, 2H), 2.63 (dd, J = 15.2, 7.6 Hz, 2H), 2.24 (s, 3H), 1.43 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.3 Hz, 3H).

Ethyl-(2*E*,4*E*,6*Z*)-3-methyl-6,7-(2,3-thienyl)-7-[3-ethyl-5-*tert*-butyl-6-(3-fluoro propoxybenzene]pentane-2,4,6-trienoate (54b). Reaction of 161 mg (0.46 mmol) of **53a** in the presence of the anion of triethyl-3-methyl-phosphonocrotonate (generated from 0.29 mL, 1.2 mmol of of triethyl-3-methyl-phosphonocrotonate and 0.6 mL of ^{n}BuLi in hexanes 1.6 M in THF-DMPU 5/0.5 mL) according to the procedure described for the synthesis of **24a** affords 208 mg (0.45 mmol, yield: 98%) of the corresponding ester **54b** as a mixture of isomers. 1H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 5.2 Hz, 1H), 7.17 (d, J = 2.0 Hz, 1H), 7.09 (d, J = 5.0 Hz, 1H), 6.97 (d, J = 15.8 Hz, 1H), 6.93 (d, J = 2.1 Hz, 1 Hz, 2H), 6.63 (d, J = 15.8 Hz, 1H), 5.85 (s, 1H), 4.45 (t, J = 6.0 Hz, 1H), 4.33 (t, J = 6.0 Hz 1H), 4.17 (dd, J = 14.3, 7.3 Hz, 2H), 3.50 (t, J = 5.8 Hz, 2H), 2.62 (dd, J = 15.1, 7.6 Hz, 2H), 2.23 (s, 3H), 1.84 (m, 1H), 1.75 (m, 1H), 1.43 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H).

(2*E*,4*E*,6*Z*)-3-Methyl-6,7-(2,3-thienyl)-7-[3-ethyl-5-*tert*-butyl-6-(2,2-difluoroethoxy benzene]pentane-2,4,6-trienoic Acid (55a). Saponification of 155 mg (0.34 mmol) of **54a** in the presence of 2 mL of LiOH (2 M aqueous solution) in a 1/1 mixture of THF/MeOH (5/5 mL) according to the procedure described for the synthesis of **25a** affords 110 mg (0.27 mmol, yield: 80%) of the desired acid **55a** as a single stereoisomer (yellow solid, mp 135 °C CH_3CN). 1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 5.2 Hz, 1H), 7.19 (d, J = 1.9 Hz, 1H), 7.11 (d, J = 5.0 Hz, 1H), 6.99 (d, J = 15.9 Hz, 1H), 6.95 (d, J = 1.9 Hz, 1H), 6.68 (d, J = 15.9 Hz, 1H), 5.89 (s, 1H), 5.63 (tt, J = 55.4, 4.2 Hz, 1H), 3.58 (m, 2H), 2.64 (dd, J = 15.2, 7.6 Hz, 2H), 2.25 (s, 3H), 1.43 (s, 9H), 0.88 (t, J = 6.5 Hz, 3H). Anal. ($C_{24}H_{28}F_2O_3S$) C, H, S. MS (EI, 70 eV) 434 m/z 434 (MH^+, 100), 451 (100), 378 (60), 360 (70), 278 (30). HRMS for $C_{24}H_{29}F_2O_3S$ (MH^+); calcd, 434.1727, found, 434.1594.

(2*E*,4*E*,6*Z*)-3-Methyl-6,7-(2,3-thienyl)-7-[3-ethyl-5-*tert*-butyl-6-(3-fluoropropoxy benzene]pentane-2,4,6-trienoic Acid (55b). Saponification of 160 mg (0.35 mmol) of **54b** in the presence of 2 mL of LiOH (2 M aqueous solution) in a 1/1 mixture of THF/MeOH (5/5 mL) according to the procedure described for the synthesis of **25a** affords 105 mg (0.26 mmol, yield: 75%) of the desired acid **55b** as a single stereoisomer (yellow solid, mp 128 °C CH_3CN). 1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 5.1 Hz, 1H), 7.17 (d, J = 2.0 Hz, 1H), 7.10 (d, J = 5.2 Hz, 1H), 7.00 (d, J = 15.8 Hz, 1H), 6.93 (d, J = 1.9 Hz, 1H), 6.65 (d, J = 15.8 Hz, 1H), 5.87 (s, 1H), 4.45 (t, J = 5.4, Hz, 1H), 4.32 (t, J = 5.4 Hz, 1H), 3.51 (m, 2H), 2.63 (dd, J = 15.2, 7.6 Hz, 2H), 2.24 (s, 3H), 1.85 (m, 1H), 1.75 (m, 1H), 1.43 (s, 9H), 1.25 (t, J = 7.5 Hz, 3H). Anal. ($C_{25}H_{31}FO_3S$) C, H, S. MS (EI, 70 eV) 430 m/z 430 (MH+, 70), 447 (100), 430 (70), 412 (95). HRMS for $C_{25}H_{32}FO_3S$ (MH^+); calcd, 430.1978, found, 430.2202.

3,5-Di-*iso*-propyl-6-(3-hydroxypropoxy)iodobenzene (56). Alkylation of 3.22 g (10.0 mmol) of **26** in the presence of 3.04 g (11.0 mmol) of 1-bromo-3-(*tert*-butyl dimethylsiloxy)-propane and 576 mg (12.0 mol) of NaH according to the

procedure described for the synthesis of **17** affords the corresponding crude protected alcohol as a clear oil. This one was directly treated with 15 mL of TBAF (1.0 M in THF) and stirred until complexion (TLC monitoring). After evaporation of the solvents, the residue was purified over silica gel column chromatography to afford 3.55 g (9.1 mmol, yield: 91%) of **56** as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 2.2 Hz, 1H), 7.33 (d, J = 2.2 Hz, 1H), 4.14 (t, J = 5.8 Hz, 2H), 3.98 (m, 2H), 2.13 (m, 2H), 1.37 (s, 9H), 1.28 (s, 9H), 0.95 (s, 9H), 0.01 (s, 6H).

3,5-Di-*iso*-propyl-6-(3-formylpropoxy)iodobenzene (57). To a mixture of 8.28 g (38.0 mmol) of PCC, 8.3 g of Celite and 8.3 g of molecular sieve in 50 mL of CH_2Cl_2 was added 3.5 g (8.96 mmol) of **56** (disolved in 15 mL of CH_2Cl_2) at RT. After complexion of the reaction (TLC monitoring), the mixture was filtrated and the solvents removed under reduced pressure. Purification of the crude oil over silica gel column chromatography (eluent: 95/5 hexane/ethyl acetate) affords 2.27 g (5.85 mol, yield: 65%) of **57** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (d, J = 1.8 Hz, 1H), δ 7.65 (d, J = 2.3 Hz, 1H), 7.33 (d, J = 2.3 Hz, 1H), 4.33 (t, J = 6.5 Hz, 2H), 3.00 (td, J = 6.5, 1.8 Hz, 2H), 1.37 (s, 9H), 1.28 (s, 9H).

3,5-Di-*tert*-butyl-6-(3,3-difluoropropoxy)iodobenzene (58). To a mixture of 2.20 g (5.66 mmol) of **57** in 30 mL of CH_2Cl_2 was added dropwise 3.1 mL (3.77 g, 23.4 mmol) of DAST. The mixture was stirred overnight at room temperature and carefully quenched with 2 N aq Na_2CO_3 solution. After extraction with CH_2Cl_2, the organic fractions were collected, dried over $MgSO_4$, filtrated and concentrated. Purification of the crude oil over SiO_2 column chromatography (eluent: hexanes/EtOAc: 95/5) affords 2.06 g (5.0 mmol, yield: 88%) of **58** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 2.1 Hz, 1H), 7.33 (d, J = 2.1 Hz, 1H), 6.21 (tt, J = 55.0, 4.3 Hz, 1H), 4.12 (t, J = 6.0 Hz, 2H), 2.40 (m, 2H), 1.37 (s, 9H), 1.28 (s, 9H).

1-[3,5-Di-*tert*-butyl-6-(3,3-difluoropropoxy)benzene]-2-formylthiophene (59). Reaction of 250.0 mg (0.61 mmol) of **58** in the presence of 114.0 mg (0.73 mmol) of boronic acid and 70.0 mg (0.061 mmol) of $Pd(PPh_3)_4$ according to the procedure described for the synthesis of **19**, affords 192.0 mg (0.49 mmol, yield: 80%) of **59** as a clear oil. (400 MHz, $CDCl_3$) δ 9.75 (d, J = 1.2 Hz, 1H), 7.79 (dd, J = 4.8 Hz, J = 1.1 Hz, 1H), 7.43 (d, J = 2.5 Hz, 1H), 7.25 (d, J = 5.0 Hz, 1H), 7.14 (d, J = 2.5 Hz, 1H), 5.83 (tt, J = 56.6, 4.7 Hz, 1H), 3.53 (m, 2H), 1.96 (m, 1H), 1.42 (s, 9H), 1.33 (s, 9H).

Ethyl-(*2E*,*4E*,*6Z*)-3-methyl-6,7-(2,3-thienyl)-7-[3,5-di-*tert*-butyl-6-(3,3-difluoropropoxybenzene]pentane-2,4,6-trienoate (60). Reaction of 192.0 mg (0.49 mmol) of **59** in the presence of the anion of triethyl-3-methyl-phosphonocrotonate (generated from 0.36 mL, 1.5 mmol of of triethyl-3-methyl-phosphonocrotonate and 0.63 mL of *n*-BuLi in hexanes 2.5 M in THF-DMPU 2.5/2.5 mL) according to the procedure described for the synthesis of **24a** affords 240.0 mg (0.47 mmol, yield: 97%) of the corresponding ester **60** as a mixture of isomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 2.5 Hz, 1H), 7.31 (d, J = 5.2 Hz, 1H), 7.11 (d, J = 5.1 Hz, 1H), 7.07 (d, J = 2.4 Hz, 1H), 6.97 (d, J = 15.9 Hz, 1H), 6.65 (d, J = 15.9 Hz, 1H), 5.86 (s, 1H), 5.82 (tt, J = 56.8 Hz, J = 4.8 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.54 (t, J = 5.8 Hz, 2H), 2.24 (s, 3H), 1.93 (m, 2H), 1.43 (s, 9H), 1.32 (s, 9H), 1.29 (t, J = 7.1 Hz, 3H).

(*2E*,*4E*,*6Z*)-3-Methyl-6,7-(2,3-thienyl)-7-[3,5-di-*tert*-butyl-6-(3,3-difluoropropoxy benzene]pentane-2,4,6-trienoic Acid (61). Saponification of 240.0 mg (0.47 mmol) of **60** in the presence of 0.75 mL of LiOH (2 M aqueous solution) in a 1/1 mixture of THF/MeOH (2.5/2.5 mL) according to the procedure described for the synthesis of **25a** affords 29.4 mg (0.061 mmol, yield: 16%) of the desired acid **61** as a single stereoisomer (yellow solid, mp 145 °C CH_3CN). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 2.4 Hz, 1H), 7.33 (d, J = 5.1 Hz, 1H), 7.12 (d, J = 5.1 Hz, 1H), 7.07 (d, J = 2.4 Hz, 1H), 7.03 (d, J = 15.9 Hz, 1H), 6.68 (d, J = 15.8 Hz, 1H), 5.88 (s, 1H), 5.82 (tt, J = 56.7, 4.8 Hz, 1H), 3.35 (t, J = 5.9 Hz, 2H), 2.25 (s, 3H), 1.94 (m, 2H), 1.42 (s, 9H), 1.32 (s, 9H). Anal. ($C_{27}H_{34}F_2O_3S\cdot$ 0.6 H_2O) C, H. MS (EI, 70 eV) 476 *m*/*z* 476 (MH^+, 40), 458 (45), 420 (45), 402 (100). HRMS for $C_{27}H_{35}F_2O_3S$ (MH^+); calcd, 476.2197, found: 476.2382.

Biology. Cotransfection Assay. All cotransfections were carried out in 96-well plates in an automated workstation with CV-1 cells as previously described by Boehm and al.[28]

Cotransfection assays were performed in CV-1 cells transfected with an expression vector for each of the RXR subtypes and a luciferase reporter gene under the control of the appropriate RXR response element (RXRE).[28] A CRBPII-tk-Luc reporter construct was used for RXRα. Similarly, for the heterodimer assay, RXRα was cotransfected into CV-1 cells along with an expression vector for hPPARγ; activation of the RXR:hPPARγ heterodimer was tested on the PPRE-tk-Luc reporter as described.[28] The luciferase reported contains three copies of the AOX PPRE driving luciferase expression. Compounds were tested in three separate experiments in log dilutions from 1×10^{-5} to 1×10^{-12} M, with triplicate determinations at each concentration. Typically, CV-1 cells were transiently cotransfected with the receptor expression vector, the receptor plasmid, and a β-galactosidase (RSV-β-Gal) internal control (used to calculate normalized lucferase response). The cells were incubated in the presence of the test compound and assayed for luciferase and β-galactosidase activity as described previously.[28] The luciferase data are presented as percent normalized response with the maximal response (100%) elicited by the control retinoid (all-*trans*-retinoic acid for the RXR assays and BRL49653 for the RXR:hPPARγ heterodimer assay). Synergy assays were performed using the same protocol except that a combination of the test compound plus the agonist of the heterodimeric partner were incubated concomitantly in the same dose−response paradigm. For the RXR:hPPARγ synergy assay, the test compound was incubated simultaneously with 100 nM of BRL49653 and for the RXR:RAR synergy assay, the test compound was incubated simultaneously with 3 nM of TTNPB.

Binding Studies. Receptor binding assays for RARs and RXRs were performed in a similar manner as described in Boehm et al. using [^{3}H]-9-cis-RA as the radioligand for RXRs, [^{3}H]-ATRA (purchased from NEN-DuPont) for the RARs.[28] Receptor binding assays for PPARs were performed in a similar manner using proprietary radioactive ligands as described in recent patent applications.[25] 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 + compound of interest. At the end of the experiments, 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 5−6 days before treatment and were dosed via oral gavage with 1 mL 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 animals were dosed by oral gavage with either vehicle alone, or a suspension of compound in the vehicle. Blood was collected from the tail vein of conscious animals. Plasma was prepared and kept frozen at −20 °C until analyzed.

Supporting Information Available: Purity of compounds **25a**, **25b**, **25c**, **31a**, **31b**, **31c**, **34**, **39a**, **39b**, **40**, **44**, **49**, **55a**, **55b**, and **61** determined by HPLC. This material is available free of charge via the Internet at http://pubs.acs.org.

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