Synthesis and Biological Evaluation of a Series of Liver-Selective Phosphonic Acid Thyroid Hormone Receptor Agonists and Their Prodrugs

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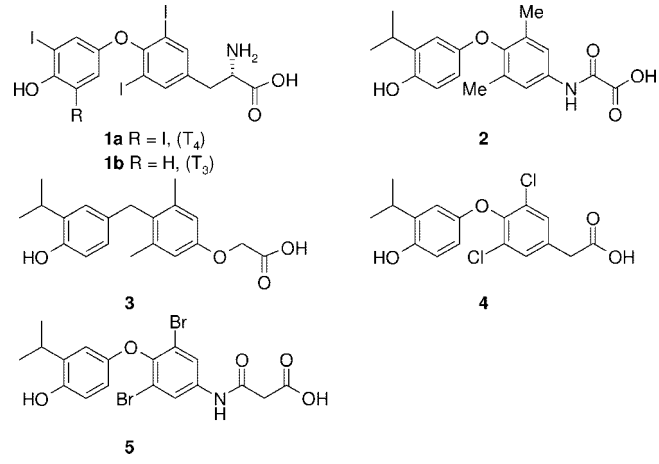
Phosphonic acid (PA) thyroid hormone receptor (TR) agonists were synthesized to exploit the poor distribution of PA-based drugs to extrahepatic tissues and thereby to improve the therapeutic index. Nine PAs showed excellent TR binding affinities (TRβ_1, K_i < 10 nM), and most of them demonstrated significant cholesterol lowering effects in a cholesterol-fed rat (CFR) model. Unlike the corresponding carboxylic acid analogue and T_3, PA **22c** demonstrated liver-selective effects by inducing maximal mitochondrial glycerol-3-phosphate dehydrogenase activity in rat liver while having no effect in the heart. Because of the low oral bioavailability of PA **22c**, a series of prodrugs was synthesized and screened for oral efficacy in the CFR assay. The liver-activated cyclic 1-(3-chlorophenyl)-1,3-propanyl prodrug (MB07811) showed potent lipid lowering activity in the CFR (ED_{50} 0.4 mg/kg, po) and good oral bioavailability (40%, rat) and was selected for development for the treatment of hypercholesterolemia.

Introduction

Dyslipidemia is a key contributor to coronary heart disease (CHD[a]),[1] the leading cause of death in the U.S.,[2] and is a growing epidemic in developed countries. A major contributor to dyslipidemia is hypercholesterolemia, which is usually attributed to high levels of low-density lipoprotein cholesterol (LDL-C) and regarded by the National Cholesterol Education Program (NCEP) as an important risk factor.[3] Currently, therapies such as hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins[4]) and agents that limit cholesterol absorption (e.g., ezetimibe,[5] bile acid sequestrants[6]) are used alone or in combination to help patients achieve the NCEP-recommended LDL-C level. While large scale clinical trials with statins have established that every 1% lowering of LDL-C resulted in an approximate 1% reduction in CHD risk,[7] many patients on statin therapy still fail to bring their LDL-C within the normal range,[8] necessitating the discovery of additional therapies having additive effects with statins.

The thyroid hormones (THs) play a critical role in growth, development, metabolism, and homeostasis.[9] They are produced by the thyroid gland as thyroxine (T_4, **1a**, Chart 1) and 3,5,3′-triiodo-L-thyronine (T_3, **1b**, Chart 1). T_4 is the major secreted form in humans and is enzymatically deiodinated by deiodinases to the more active form, T_3, in peripheral tissues. THs exert their action by interacting with thyroid hormone receptors (TRs), which belong to the nuclear hormone receptor superfamily, and regulate the transcription of target genes.[10] TRs are expressed in most tissues and exist as two isoforms (TRα and TRβ) that are expressed predominantly as the alternatively spliced variants TRα_1 and TRβ_1. Tissue distribution studies,[9] mouse knockout studies,[11] and evaluation of patients with resistance to thyroid hormone (RTH) syndrome[12] have established that TRα_1 is the predominant isoform in the heart and regulates most cardiac functions, while the TRβ_1 isoform predominates in the liver and the pituitary and regulates cholesterol metabolism and thyroid-stimulating hormone (TSH) production, respectively.

Chart 1. Structures of TR Ligands



In recognition of the potential benefits associated with modulation of TRs, numerous approaches have been pursued to identify a suitable TR agonist. Initial studies with T_3 and T_4 in humans demonstrated their usefulness in lowering plasma cholesterol levels.[13] However, these benefits were offset by deleterious cardiovascular side effects (tachycardia, arrhythmia).[14] Consequently, more recent approaches focused on the identification of TR agonists that bind preferentially to the TRβ_1.[15] *N*-[3,5-Dimethyl-4-(4′-hydroxy-3′-isopropylphenoxy)phenyl]oxamic acid (CGS 23425, **2**) showed preferential

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[a] Abbreviations: CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; HMG-CoA, hydroxymethylglutaryl coenzyme A; TH, thyroid hormone; T_4, thyroxine or 3,5,3′,5′-tetraiiodo-L-thyronine; T_3, 3,5,3′-triiodo-L-thyronine; TR, thyroid hormone receptor; RTH, resistance to thyroid hormone; TSH, thyroid-stimulating hormone; TI, therapeutic index; PA, phosphonic acid; TPC, total plasma cholesterol; mGPDH, mitochondrial glycerol-3-phosphate dehydrogenase; TRIAC, 3,5-diiodo-4-(4′-hydroxy-3′-iodophenoxy)phenylacetic acid; HPT, hypothalamic−pituitary−thyroid.

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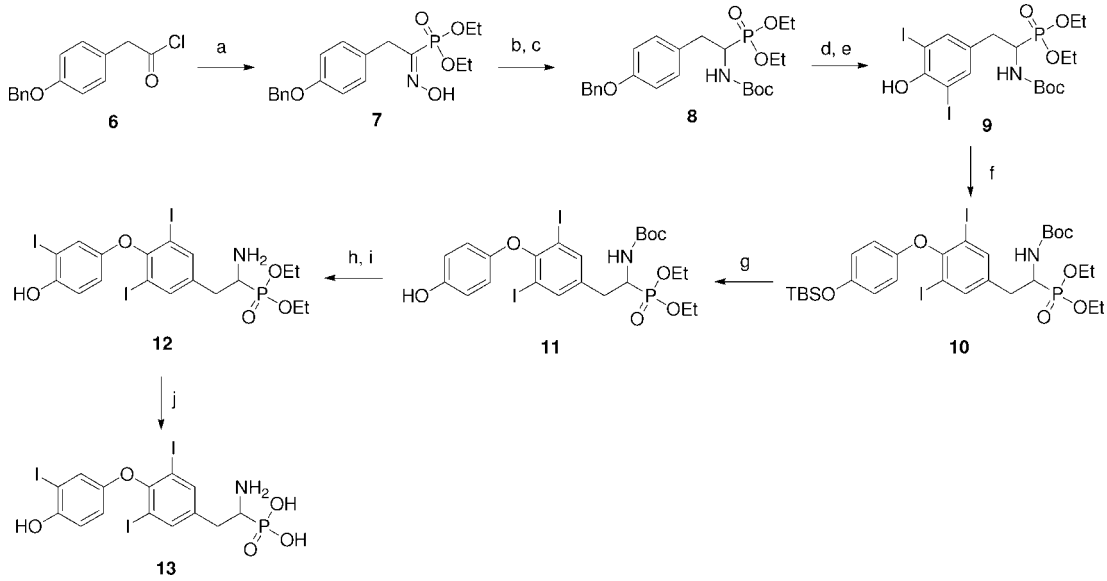
Scheme 1[a]



[a] Reagents and conditions: (a) (1) $P(OEt)_3$, THF; (2) NH_2OH, pyridine, room temp, 85% for two steps; (b) $NaBH_4$, $NiCl_2$, MeOH, room temp; (c) $(Boc)_2O$, THF, room temp, 46% for two steps; (d) H_2, Pd−C, MeOH; (e) $I(Py)_2BF_4$, CH_2Cl_2, 0 °C to room temp, 88% for two steps; (f) 4-(*tert*-butyldimethylsilyloxy)phenylboronic acid, $Cu(OAc)_2$, Et_3N, CH_2Cl_2, room temp, 60%; (g) TBAF, THF, room temp, 62%; (h) 70% aqueous TFA, room temp; (i) I_2, KI, $MeNH_2$, EtOH, 0 °C, 69% for two steps; (j) TMSBr, CH_2Cl_2, −30 °C to room temp, 95%.

binding to the rat liver nuclear TR over plasma membrane TR[16] and was later found to be a TRβ_1-selective TR agonist.[17] Compound **2** demonstrated good lipid lowering effects in hypercholesterolemic rats without cardiac side effects.[17] Scanlan's group identified 3,5-dimethyl-4-(4′-hydroxy-3′-isopropylbenzyl)phenoxyacetic acid (GC-1, **3**) and showed it to be 10 times more selective toward human TRβ_1 than TRα_1.[18] TR agonist **3** exhibited a rightward shift (20-fold) of the dose response for heart rate compared to the dose response for cholesterol lowering in hypercholesterolemic rats.[19] In addition, **3** shows a higher level of uptake in the liver versus heart that may further contribute to the cardiac sparing effect observed in vivo.[20] In 2003, 3,5-dichloro-4-(4′-hydroxy-3′-isopropylphenoxy)phenylacetic acid (KB-141, **4**) was reported by Karo Bio to have 14-fold higher affinity toward human TRβ_1 than TRα_1.[21] In primate studies, TR agonists **4** lowered both plasma cholesterol and body weight at doses that did not affect heart rate.[22] On the basis of these preclinical data, **3**[23] and the recently disclosed TR agonist [3,5-dibromo-4-(4′-hydroxy-3′-isopropylphenoxy)phenylamino]-3-oxopropanoic acid (KB-2115, **5**)[24] were evaluated in humans, and both compounds lowered LDL-C and were generally well tolerated. However, the long-term effects of these carboxylic acids are unknown because the TRβ_1-selective agonists **3**[20] and **4**[22] do not show a separation between cholesterol lowering vs thyroid stimulating hormone (TSH) lowering, a process mediated by TRβ_1 in the pituitary.[10]

In contrast to the traditional approach focusing on TRβ_1-selective ligands, our strategy revolved around developing TR agonists that would selectively be transported into the liver and consequently avoid TR activation in the pituitary or in the heart.[25]Since TRβ_1 is highly expressed in the liver,[10] we envisioned that liver-targeted TR agonists would retain lipid lowering effects but would have fewer side effects in extrahepatic tissues than any of the synthetic TR agonists described to date.[18,21] Since phosphonic acids (PAs) are highly charged molecules at physiological pH and usually have limited tissue distribution outside the liver and kidney, where organic anion transporters are highly expressed,[26] we hypothesized that PA ligands would achieve liver-specific TR activity if those compounds could bind to human TR with sufficient affinity. Moreover, their liver specificity could potentially be enhanced by use of liver-targeting prodrugs developed in our laboratories.[27] Thus, we synthesized a series of PAs that incorporated key structural elements considered important for TR binding affinity and evaluated their structure−activity relationships with respect to TR binding affinity, in vivo cholesterol lowering efficacy, and TR agonist activity in the liver and heart. Results from these studies led to the identification of the liver-selective TR agonist **22c.**

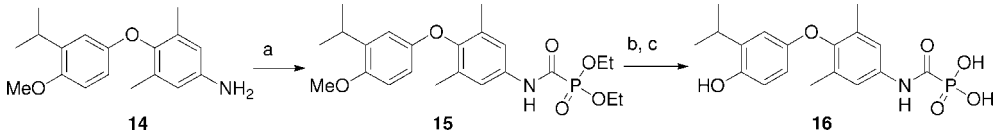
Unlike the carboxylic acid-containing TR agonists, **22c** exhibited low oral bioavailability in rats and monkeys based on plasma levels. Consequently, we investigated a variety of phosphonate prodrugs[29] to assess their ability to enhance oral bioavailability, including acyloxyalkyl esters,[30] alkoxycarbonyloxyalkyl esters,[31] *S*-acylthioethyl esters,[32] diphenyl esters,[33] phosphonic diamides,[34] and cyclic 1-(aryl)-1,3-propanyl (HepDirect)[27] prodrugs. To avoid activation of the prodrug in extrahepatic tissues and the associated side effects, we searched for either prodrugs that undergo rapid prodrug cleavage in the plasma to **22c**, which then selectively distributes to the liver, or prodrugs with hepatocyte-specific cleavage to **22c**. These efforts led to the selection of the cyclic 1-(aryl)-1,3-propanyl prodrug class, which is the only known prodrug class that combines stability in extrahepatic tissue with selective activation in hepatocytes, giving it liver-targeting capability.

The present report discloses the synthesis and SAR of a series of phosphonic acid TR agonists, as well as an orally bioavailable prodrug of **22c**, **72** (MB07811), that shows potent oral efficacy in the cholesterol-fed rat.

Chemistry

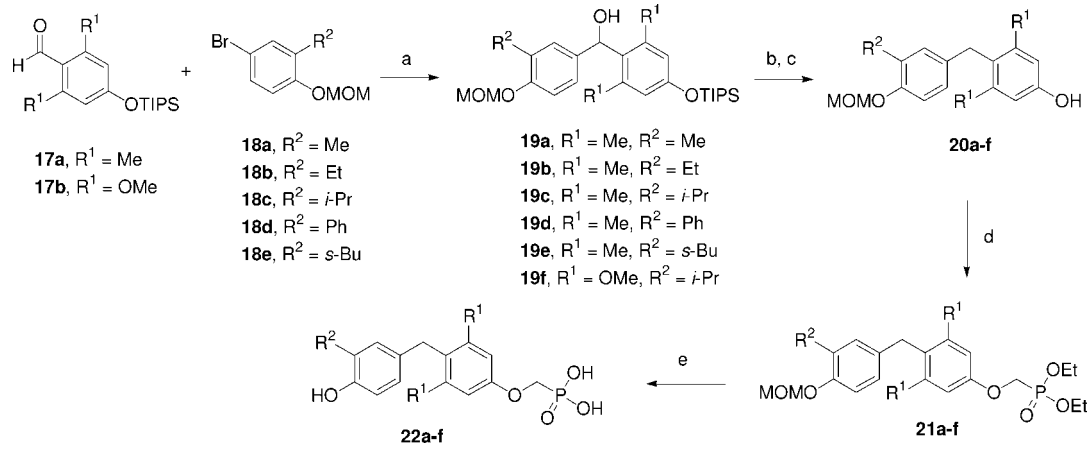
A series of phosphonic acids containing the structural backbones of known carboxylic acid ligands were synthesized. As described in Scheme 1, the T_3 analogue was prepared from commercially available 4-benzyloxyphenylacetyl chloride **6**. Michaelis−Arbuzov reaction[35] with triethyl phosphite followed by treatment of the resulting ketophosphonate with hydroxy-

Scheme 2[a]



[a] Reagents and conditions: (a) (1) diphosgene, dioxane, room temp to 60 °C; (2) $HP(O)(OEt)_2$, Et_3N, hexanes, room temp to 80 °C, 64% for two steps; (b) TMSBr, CH_2Cl_2, −30 °C to room temp; (c) BBr_3, CH_2Cl_2, −78 °C to room temp, 42% for two steps.

Scheme 3[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 °C, 60−85%; (b) H_2, Pd−C, AcOH−EtOAc, room temp; (c) TBAF, THF, 0 °C to room temp, 85% for two steps; (d) $TfOCH_2P(O)(OEt)_2$, Cs_2CO_3 or $TsOCH_2P(O)(OEt)_2$, NaH, DMF, room temp, 60−80%; (e) TMSBr, CH_2Cl_2, −30 °C to room temp, 90−100%.

lamine generated oxime **7**.[36] Reduction with sodium borohydride in the presence of nickel chloride[37] followed by treatment with di-*tert*-butyl dicarbonate gave **8**, which was converted to phenol **9** by hydrogenolysis and iodination with bis(pyridine)iodonium tetrafluoroborate. Coupling of **9** with 4-(*tert*-butyldimethylsilyloxy)phenylboronic acid in the presence of copper acetate afforded biaryl ether **10**, which was deprotected to give phenol **11**. Removal of the *tert*-butoxycarbonyl protecting group followed by monoiodination with iodine and potassium iodide yielded phosphonate **12**. Deprotection with trimethylsilyl bromide provided the T_3 phosphonic acid analogue **13**. The phosphonic acid analogue of **3** was prepared from aniline **14**[16] (Scheme 2). Treatment of **14** with diphosgene followed by diethyl phosphite provided phosphonate **15**,[38] which was deprotected as described above to give phosphonic acid **16**.

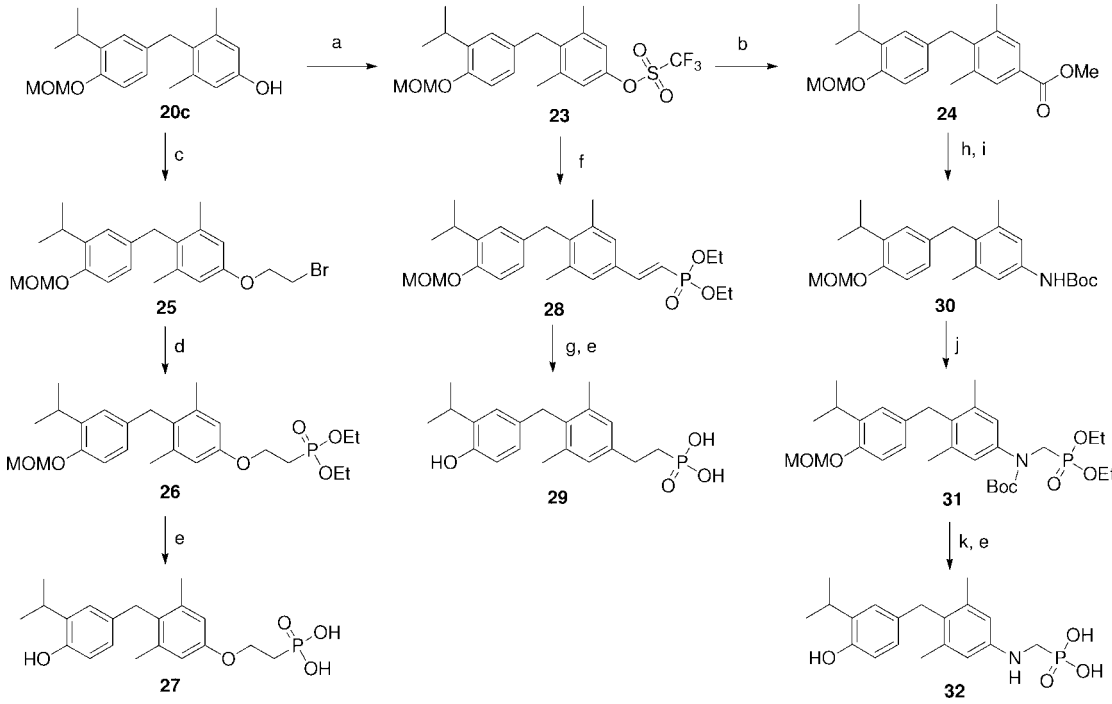
As outlined in Scheme 3, phosphonic acids based on TR agonist **3** (benzylphenyl series) were synthesized from the triisopropylsilyl-protected benzaldehydes **17a**,**b** and the methoxymethyl-protected phenols **18a**−**e**, both of which were prepared from commercially available starting materials according to the known procedures.[39] Treatment of **18a**−**e** with *n*-butyllithium at −78 °C followed by coupling with **17a**,**b** generated benzyl alcohols **19a**−**f**, which were converted to phenols **20a**−**f** by hydrogenolysis and deprotection with tetrabutylammonium fluoride. The phosphonate moiety was introduced by alkylation of phenols **20a**−**f** with diethyl tosyloxymethylphosphonate (or diethyl trifluoromethylsulfonyloxymethylphosphonate) in the presence of cesium carbonate or sodium hydride to provide phosphonates **21a**−**f** in 60−80% yield. Final deprotection of **21a**−**f** with trimethylsilyl bromide led to phosphonic acids **22a**−**f**.

Previous studies in the field demonstrated the importance of the linker between the carboxylic acid and the phenyl group on the binding affinity.[16,40] To explore this effect in the phosphonic acid series, analogues **27**, **29**, and **32** were synthesized. As described in Scheme 4, coupling of phenol **20c** with 1,2-dibromoethane provided **25**. Introduction of the phosphonate by Michaelis−Arbuzov reaction generated **26**, which was deprotected with trimethylsilyl bromide to afford phosphonic acid homologue **27**. Also, treatment of **20c** with triflic anhydride yielded triflate **23**, which underwent a Heck reaction with diethyl vinylphosphonate in the presence of tetrakis(triphenylphosphine)palladium to give phosphonate **28**. Hydrogenation followed by deprotection with trimethylsilyl bromide led to phosphonic acid **29**. Alternatively, triflate **23** was converted to methyl benzoate **24** by palladium-catalyzed carbonylation. Treatment of **24** with sodium hydroxide followed by Curtius rearrangement with diphenylphosphoryl azide in *tert*-butanol generated the *tert*-butoxycarbonyl-protected aniline **30**.[41] Introduction of the phosphonate moiety with diethyl trifluoromethylsulfonyloxymethylphosphonate yielded **31**, which was deprotected with hydrogen chloride and trimethylsilyl bromide to provide phosphonic acid **32**.

Phosphonic acids based on TR agonist **4** (diphenyl ether series) were constructed from the appropriate phenols and bis(3-isopropyl-4-methoxyphenyl)iodonium tetrafluoroborate **33** according to the known methods.[16,21] As shown in Scheme 5, coupling of phenols **34a**−**c** with **33** provided methyl benzoates **35a**−**c**, which were converted to benzyl bromides **36a**−**c** by reduction with diisobutylaluminum hydride followed by treatment of the resulting benzyl alcohols with carbon tetrabromide and triphenylphosphine. **36a**−**c** were reacted with triethyl phosphite to provide phosphonates **37a**−**c**, which were deprotected with trimethylsilyl bromide followed by boron tribromide to afford phosphonic acids **38a**−**c**. In addition, **36c** (R^1 = Br) was reacted with diethyl methylphosphonate to yield phosphonate **39**,[42] which was deprotected as described above to generate phosphonic acid **40**.

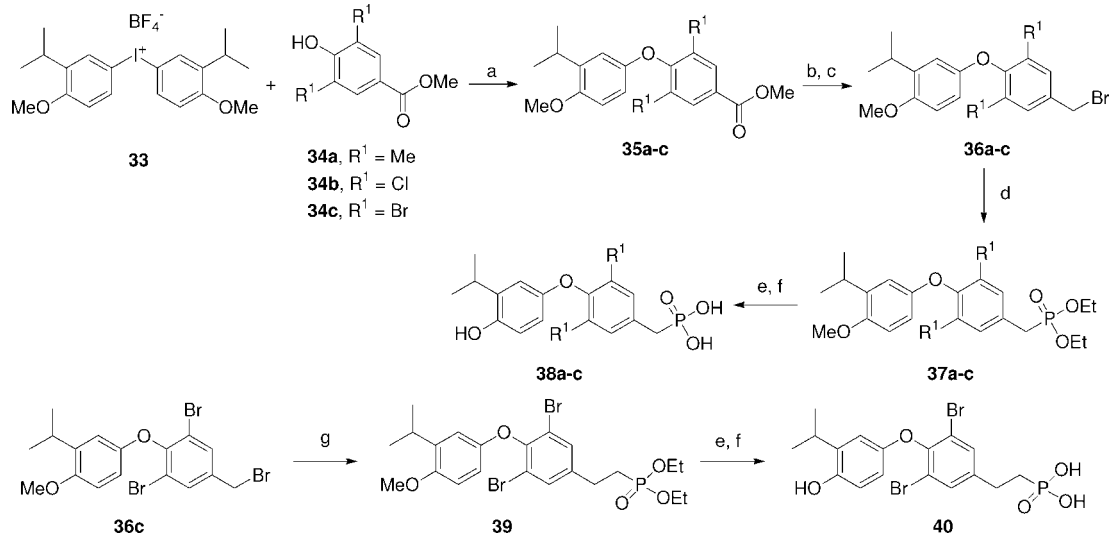
The triiodo and diiodo analogues were prepared from benzyl bromide **41**[43] as illustrated in Scheme 6. Benzyl bromide **41** underwent Michaelis−Arbuzov reaction with triethyl phosphite followed by hydrogenolysis to give phenol **42**, which was

Scheme 4[a]



[a] Reagents and conditions: (a) Tf_2O, DMAP, CH_2Cl_2, 0 °C, 100%; (b) CO (60 psi), $Pd(OAc)_2$, 1,3-bis(diphenylphosphino)propane, Et_3N, MeOH−DMF, 90 °C, 93%; (c) $BrCH_2CH_2Br$, Cs_2CO_3, DMF, 60 °C, 16%; (d) $P(OEt)_3$, DMF, 140 °C, 50%; (e) TMSBr, CH_2Cl_2, −30 °C to room temp; (f) diethyl vinylphosphonate, $Pd(PPh_3)_4$, DMF, 90 °C, 45%; (g) H_2, Pd−C, MeOH, room temp, 100%; (h) NaOH, MeOH, 50 °C, 98%; (i) diphenylphosphoryl azide, Et_3N, *tert*-butanol, 80 °C, 75%; (j) $TfOCH_2P(O)(OEt)_2$, LDA, THF, 0 °C to room temp, 49%; (k) 2 N HCl, MeOH, room temp, 51%.

Scheme 5[a]

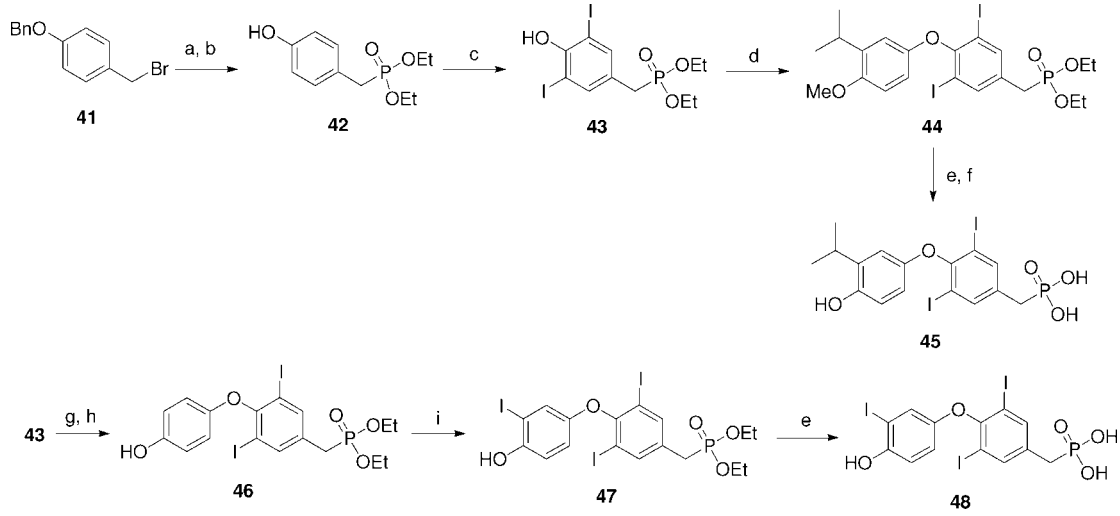


[a] Reagents and conditions: (a) Cu, Et_3N, CH_2Cl_2, 0 °C to room temp, 80%; (b) DIBAL-H, THF, 0 °C; (c) CBr_4, PPh_3, Et_2O, room temp, 54% for two steps; (d) $P(OEt)_3$, DMF, 120 °C, 85%; (e) TMSBr, CH_2Cl_2, −30 °C to room temp; (f) BBr_3, CH_2Cl_2, −78 °C to room temp, 40−80% for two steps; (g) $CH_3P(O)(OEt)_2$, THF, LDA, −78 °C to room temp, 43%.

converted to diiodophenol **43** upon treatment with bis(pyridine)iodonium tetrafluoroborate.[44] Coupling with iodonium salt **33** yielded biaryl ether **44**, which was deprotected with trimethylsilyl bromide and boron tribromide to generate phosphonic acid **45**. Also, **43** was reacted with 4-(*tert*-butyldimethylsilyloxy)phenylboronic acid in the presence of copper acetate followed by deprotection with tetrabutylammonium fluoride to provide phenol **46**.[45] Monoiodination of **46** with iodine and potassium iodide led to **47**, which was deprotected with trimethylsilyl bromide to give the triiodo-substituted phosphonic acid **48**.

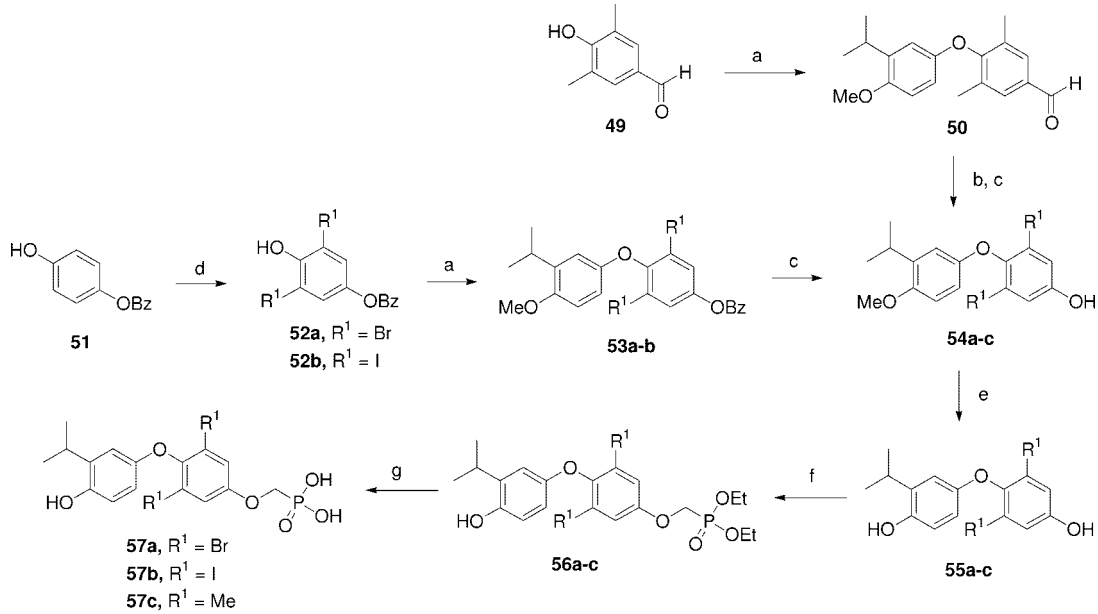
Several analogues with an oxygen-connected side chain were prepared as outlined in Scheme 7. Coupling of 3,5-dimethyl-4-hydroxylbenzaldehyde **49** with iodonium salt **33** gave benzaldehyde **50**, which was reacted with 3-chloroperoxybenzoic acid followed by treatment with sodium hydroxide to provide phenol **54c**. Alternatively, either bromination or iodination of commercially available phenol **51** gave the substituted phenols **52a**,**b**. Coupling with iodonium salt **33** provided biaryl ethers **53a**,**b**, which were converted to phenols **54a**,**b** after alkaline hydrolysis with sodium hydroxide. Deprotection of **54a**−**c** with boron tribromide gave diphenols **55a**−**c**. Selective alkylation

Scheme 6[a]



[a] Reagents and conditions: (a) $P(OEt)_3$, DMF, 120 °C; (b) H_2, Pd−C, MeOH, room temp, 84% for two steps; (c) $I(Py)_2BF_4$, CH_2Cl_2, 0 °C to room temp, 90%; (d) **33**, Cu, Et_3N, CH_2Cl_2, 0 °C to room temp, 85%; (e) TMSBr, CH_2Cl_2, −30 °C to room temp, (f) BBr_3, CH_2Cl_2, −78 °C to room temp, 92% for two steps; (g) 4-(*tert*-butyldimethylsilyloxy)phenylboronic acid, $Cu(OAc)_2$, CH_2Cl_2, room temp; (h) TBAF, THF, room temp, 13% for two steps; (i) I_2, KI, $MeNH_2$, MeOH, 0 °C, 69%.

Scheme 7[a]



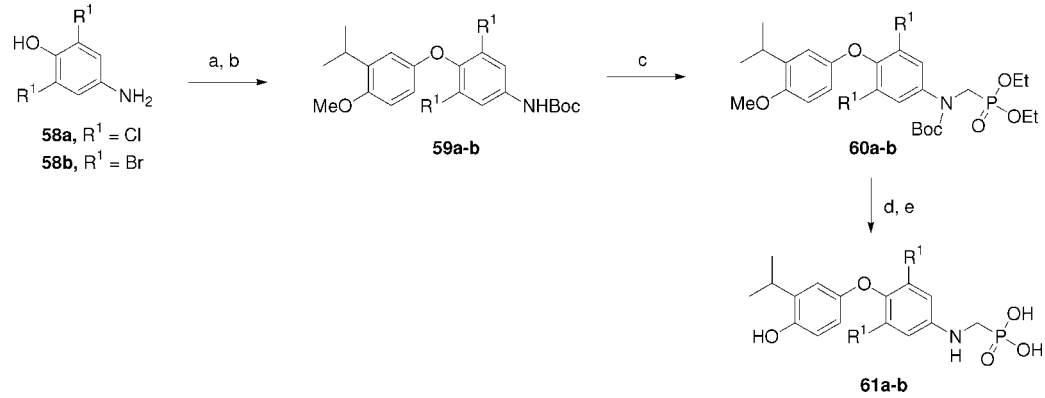
[a] Reagents and conditions: (a) Cu, **33**, Et_3N, CH_2Cl_2, 0 °C to room temp, 98−100%; (b) *m*-CPBA, room temp, 47%; (c) NaOH, MeOH, room temp, 95%; (d) $[CH_3(CH_2)_3]_4NBr_3$, CH_2Cl_2, room temp, 75% (for **52a**) or $I(Py)_2BF_4$, CH_2Cl_2, 0 °C to room temp, 84% (for **52b**); (e) BBr_3, CH_2Cl_2, −78 °C to room temp, 66%; (f) $TfOCH_2P(O)(OEt)_2$, Cs_2CO_3, DMF, room temp, 55%; (g) TMSBr, CH_2Cl_2, −30 °C to room temp, 63%.

with diethyl trifluoromethylsulfonyloxymethylphosphonate yielded phosphonates **56a**−**c** as the only products in 34−70% yield. Final deprotection with trimethylsilyl bromide led to phosphonic acids **57a**−**c**.

Two analogues with a nitrogen-connected side chain were synthesized as described in Scheme 8. Treatment of commercially available phenols **58a**,**b** with di-*tert*-butyl dicarbonate followed by coupling with iodonium salt **33** yielded biaryl ethers **59a**,**b**. Alkylation with diethyl trifluoromethylsulfonyloxymethylphosphonate gave phosphonates **60a**,**b**, which were deprotected with trimethylsilyl bromide followed by boron tribromide to provide phosphonic acids **61a**,**b**. An analogue with a sulfur-connected side chain was also prepared as outlined in Scheme 9. Treatment of **62** with *n*-butyllithium followed by dimethyl disulfide gave thioanisole **63** in excellent yield.[46] Treatment with *N*-chlorosuccinimide followed by Michaelis−Arbuzov reaction with triethyl phosphite generated phosphonate **64**.[47] Deprotection with tetrabutylammonium fluoride afforded phenol **65**. Coupling with iodonium salt **33** led to **66**, which was converted to phosphonic acid **67** by treatment with trimethylsilyl bromide and boron tribromide.

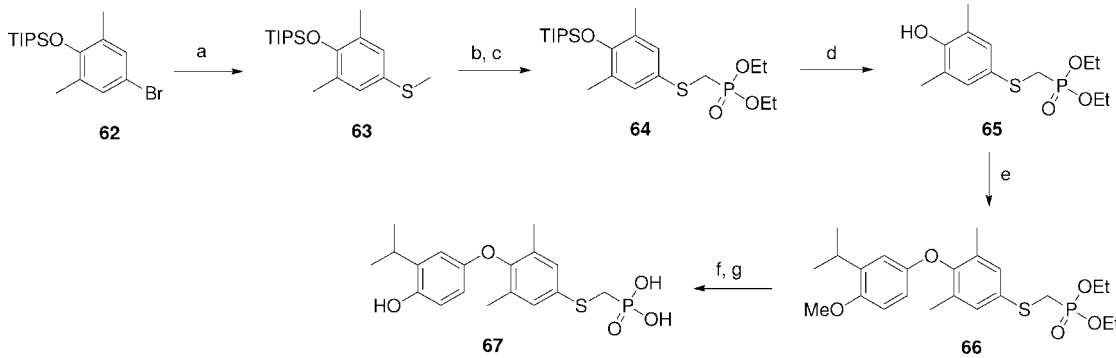
Prodrugs of phosphonic acid TR agonist **22c** were synthesized in one step according to known procedures. Alkylation with pivaloyloxymethyl iodide[48] or alkoxycarbonyloxymethyl iodide[33] provided the corresponding bis(pivaloyloxymethyl) (bis-POM) (**68**, Scheme 10) and bis-alkoxycarbonyloxymethyl prodrugs (**69**, **70**) in good yield. Dicyclohexyldiimide-mediated coupling of *S*-acetylthioethan-2-ol provided the corresponding bis-*S*-acetylthioethyl prodrug (SATE, **71**) in 56% yield. Use of the same procedure with 1-aryl-1,3-propane diols[49] provided

Scheme 8[a]



[a] Reagents and conditions: (a) $(Boc)_2O$, CH_2Cl_2, 93%; (b) **33**, Et_3N, Cu, CH_2Cl_2, 0 °C to room temp, 95%; (c) $TfOCH_2P(O)(OEt)_2$, NaH, THF, room temp, 63−70%; (d) TMSBr, CH_2Cl_2, −30 °C to room temp; (e) BBr_3, −78 °C to room temp, 85−91% for two steps.

Scheme 9[a]



[a] Reagents and conditions: (a) *n*-BuLi, Me_2S_2, THF, −78 °C to room temp, 100%; (b) NCS, CCl_4, room temp; (c) $P(OEt)_3$, 180 °C, 52% for two steps; (d) TBAF, THF, room temp, 85%; (e) Cu, **33**, Et_3N, CH_2Cl_2, 0 °C to room temp, 60%; (f) TMSBr, CH_2Cl_2, −30 °C to room temp; (g) BBr_3, CH_2Cl_2, −78 °C to room temp, 51% for two steps.

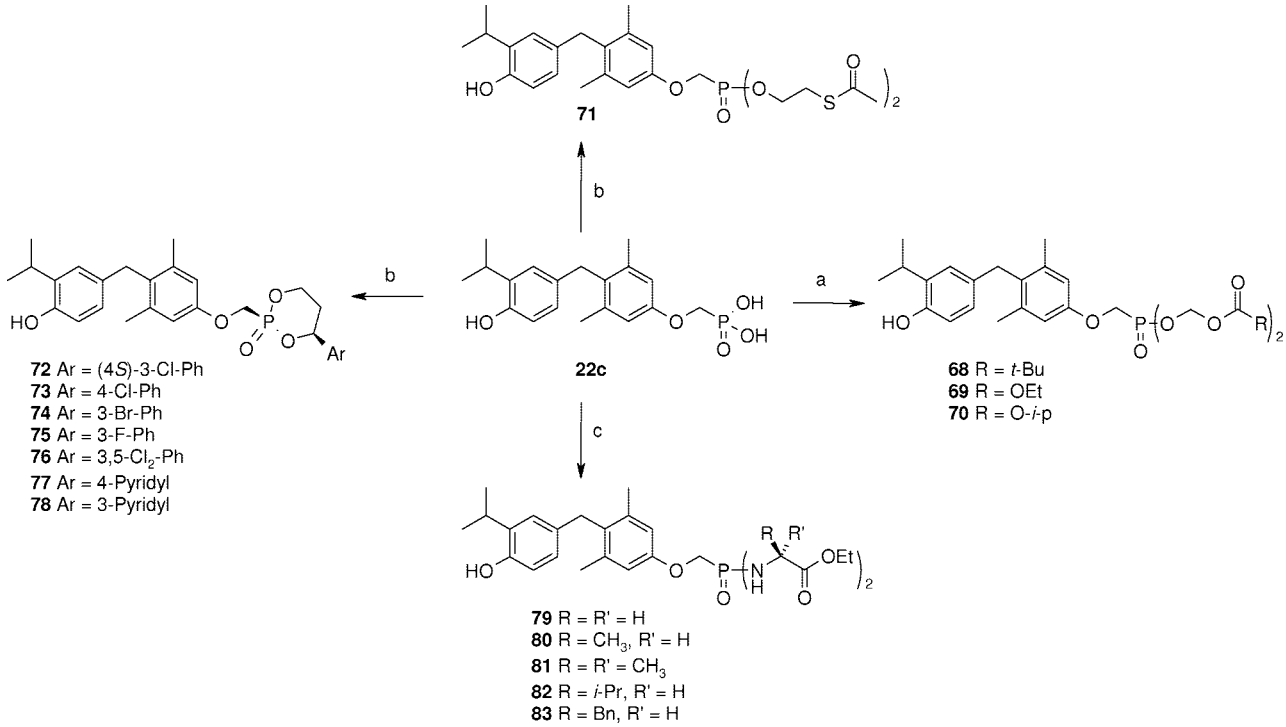
cis cyclic 1-(aryl)-1,3-propanyl prodrugs **72**−**78** in 20−40% yield after removal of the undesired trans isomer by column chromatography. Phosphonic diamide prodrugs were synthesized by generating the phosphonyl dichloride with oxalyl chloride followed by diamide formation with the corresponding amino acid ethyl ester to give phosphonic diamides[34] **79**−**83** in 20−52% yield.

Results

Receptor Binding Affinity. All phosphonic acids described above were tested in a receptor binding assay expressing human TRα_1 and TRβ_1. The results are summarized in Table 1. Unexpectedly, the phosphonic acid analogues **16** (TRβ_1, K_i = 36.0 nM; unless otherwise specified, all following binding affinities are for TRβ_1) and **13** (K_i = 271 nM) showed considerably reduced binding activity when compared to their corresponding carboxylic acids **2** (K_i = 0.47 nM) and **1b** (K_i = 0.68 nM), respectively. However, the phosphonic acid analogue **22c** displayed potent binding affinity toward human TRβ_1 (K_i = 2.95 nM), though its activity was 9-fold weaker than that of **3** (K_i = 0.32 nM). To explore the SAR in this series, we synthesized several analogues with different moieties on the ring and side chain. Among these compounds (X = CH_2, Y = OCH_2), the 3′-subsitutents (R^2) had a major impact on the binding potency. Consistent with previous reports for carboxylic acid ligands,[50,51] the binding affinity increased in the order of methyl (**22a**), ethyl (**22b**), and isopropyl (**22c**) groups. The *sec*-butyl group (**22e**) was also well tolerated at this position. As expected, the 3′-phenyl analogue (**22d**, K_i = 106 nM) showed low binding affinity. This is probably due to the lack of the necessary structural flexibility as observed in other TR ligands.[52] Moreover, the length of the side chain (Y group) also had a significant effect on binding potency. The binding affinity of homologue **27** (K_i = 87 nM) was 30-fold lower than that of **22c** (K_i = 2.95 nM). Replacement of oxygen between the phenyl ring and the side chain with nitrogen (**32**, K_i = 9.10 nM) or methylene (**29**, K_i = 31.3 nM) also decreased the binding potency. Not surprisingly, low binding affinity was observed for analogue **22f** (R^1 = OMe, K_i = 146 nM).

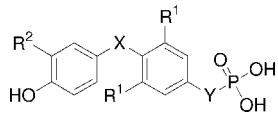
While analogue **38b** (K_i = 52.3 nM) only showed moderate binding affinity, the 3,5-diiodo-substituted phosphonic acids **45** (X = O, Y = CH_2, K_i = 0.84 nM) and **57b** (X = O, Y = OCH_2, K_i = 0.97 nM) displayed excellent binding potency. In agreement with observations for TR agonist **4** and its analogues,[21] the substituents on the inner ring (R^1) exerted a significant effect on the binding potency with the order being I > Br > Cl > Me. To explore the effects of the side chain in this series, we prepared compounds **40** (Y = CH_2CH_2), **57a** (Y = OCH_2), and **61b** (Y = $NHCH_2$). Contrary to the observations made in the benzylphenyl series, these compounds had similar binding potency. In addition, the analogue with a sulfur connected side chain (**67**, K_i = 42.1 nM) showed similar potency when compared to the compound with an oxygen connected side chain (**57c**, K_i = 25.4 nM). Interestingly, the triiodo-substituted analogue (**48**, R^1 = I, R^2 = I, K_i = 26 nM) was the only compound that showed better binding affinity toward TRα_1 than TRβ_1, though its activity was 30-fold weaker when compared to compound **45** (R^1 = I, R^2 = *i*-Pr, K_i = 0.84 nM).

Scheme 10. Synthesis of Prodrugs of Compound **22c**[a]



[a] Reagents and conditions: (a) *i*-Pr_2NEt, CH_3CN, $ICH_2OC(O)R$, room temp; (b) *S*-acetyl-2-thioethanol or 1-aryl-1,3-propane diol, pyridine, DMF, dicyclohexylcarbodiimide, 70 °C; (c) (i) $(COCl)_2$, CH_2Cl_2, DMF, 50 °C; (ii) *i*-Pr_2NEt, $H_2N-C(RR')-COOEt$, CH_2Cl_2, 0 °C.

Table 1. Binding Affinities for Human TR



compd	R^1	R^2	X	Y	TRα_1 K_i[a]	TRβ_1 K_i[a]
1b					0.33	0.68
2					0.51	0.47
3					1.09	0.32
4					7.79	0.24
13	I	I	O	$CH_2CH(NH_2)$	1416	271
16	Me	*i*-Pr	O	NHCO	285	36.0
22a	Me	Me	CH_2	OCH_2	897	89.7
22b	Me	Et	CH_2	OCH_2	61.6	9.72
22c	Me	*i*-Pr	CH_2	OCH_2	35.2	2.95
22d	Me	Ph	CH_2	OCH_2	1165	106
22e	Me	*s*-Bu	CH_2	OCH_2	30.5	6.64
22f	OMe	*i*-Pr	CH_2	OCH_2	3296	146
27	Me	*i*-Pr	CH_2	OCH_2CH_2	594	87.0
29	Me	*i*-Pr	CH_2	CH_2CH_2	378	31.3
32	Me	*i*-Pr	CH_2	$NHCH_2$	28.4	9.10
38a	Me	*i*-Pr	O	CH_2	1760	128
38b	Cl	*i*-Pr	O	CH_2	303	52.3
38c	Br	*i*-Pr	O	CH_2	235	15.5
40	Br	*i*-Pr	O	CH_2CH_2	42.1	2.50
45	I	*i*-Pr	O	CH_2	1.84	0.84
48	I	I	O	CH_2	16.0	26.0
57a	Br	*i*-Pr	O	OCH_2	18.6	2.51
57b	I	*i*-Pr	O	OCH_2	3.74	0.97
57c	Me	*i*-Pr	O	OCH_2	183	25.4
61a	Cl	*i*-Pr	O	$NHCH_2$	186	30.5
61b	Br	*i*-Pr	O	$NHCH_2$	10.3	1.51
67	Me	*i*-Pr	O	SCH_2	143	42.1

[a] K_i values are calculated means from duplicate measurements of IC_{50} using the Cheng−Prushoff equation and expressed as nM.

The role of the bridging moiety between the phenyl rings and side chain in influencing binding affinity has been well studied for the carboxylic acid TR ligands.[53] Consistent with the SAR trend for TR agonist **3** and its ether analogue, compound **22c** (X = CH_2, Y = OCH_2, K_i = 2.95 nM) demonstrated greater binding activity when compared to **57c** (X = O, Y = OCH_2, K_i = 25.4 nM).

Table 2. Cholesterol Lowering Activity of Selected Compounds

compd	% change of TPC,[a] mean ± SEM
vehicle	−5.0 ± 2.2
22b	−7.5 ± 6.1
22c	−37.2 ± 2.3
22e	−20.1 ± 12.4
32	−32.3 ± 5.6
40	−34.5 ± 2.7
45	−39.4 ± 3.1
57a	−42.6 ± 6.7
57b	−44.7 ± 8.2
61b	−47.7 ± 5.0

[a] Cholesterol-fed rats were treated by intraperitoneal injection with 0.2 mg/kg of the indicated compounds. The percentage change in total plasma cholesterol from pretreatment levels was calculated on a pairwise basis based on the total plasma cholesterol levels measured 24 h after treatment. Data represent mean values ± SEM, $n = 6$.

Effects on Total Plasma Cholesterol. Nine phosphonic acids with potent binding affinities (K_i < 10 nM) were evaluated in the cholesterol-fed rat model for their potential TR agonist effects. Each compound was administered by intraperitoneal injection at 0.2 mg/kg, and total plasma cholesterol (TPC) was measured after 24 h. The results are summarized in Table 2. Compound **22c**, the most potent compound from the benzylphenyl series, showed a 37% reduction of TPC. Surprisingly, compound **22b** did not have any cholesterol lowering effect, suggesting the rapid metabolism of this compound or a lack of agonist activity. All five diphenyl ether analogues lowered TPC more than 30%, with **61b** showing almost 48% reduction of TPC.

Effects on Heart and Liver mGPDH. In an effort to understand whether these phosphonic acids indeed have tissue-

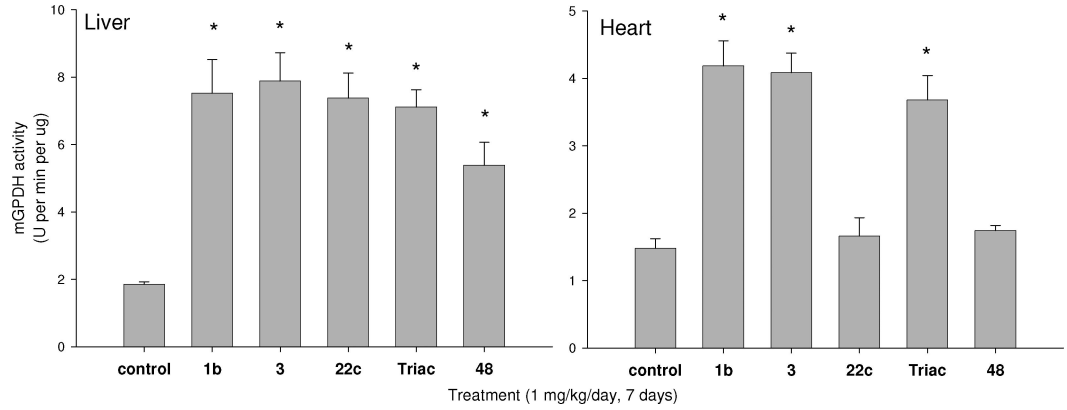


Figure 1. Effects of 7-day treatment with selected TR-agonists on liver or heart mGPDH activity. Normal rats were infused with the indicated TR-agonists at a dose of 1 (mg/kg)/day. Data represent mean values ± SEM, $n = 6$.

selective TR agonist effects, compounds **22c** and **48** and their corresponding carboxylic acid analogues **3** and 3,5-diiodo-4-(4′-hydroxy-3′-iodophenoxy)phenylacetic acid (TRIAC) were tested by chronic infusion into normal Sprague−Dawley rats. TR agonist activity in the liver and heart was assessed by measuring the activity of mitochondrial glycerol-3-phosphate dehydrogenase (mGPDH), an enzyme known to be induced by T_3.[54,55] The use of mGPDH activity permitted the comparison of TR agonist activity of all compounds using the same end point in both organs. Compounds were administered by osmotic pump infusion at a dose of 1 (mg/kg)/day for 7 days. The dose of T_3 chosen for the experiment had been used to produce cardiac changes consistent with overt hyperthyroidism in euthyroid rats.[56] Results are shown in Figure 1. Both the carboxylic acid and the phosphonic acid analogues induced liver mGPDH to the levels not significantly different from those observed in the T_3-treated animals. On the other hand, no significant increase in heart mGPDH activity was observed for the phosphonic acid analogues, while the carboxylic acid analogues induced cardiac mGPDH activity to the levels observed with T_3.

Prodrug Evaluation. Prodrugs **68**−**83** were evaluated for their ability to lower cholesterol orally (po) in vivo in the cholesterol-fed rat assay over 24 h at a dose of 0.5 mg/kg (Table 3). All esterase-sensitive prodrugs (**68**−**70**) decreased cholesterol levels in the 20−33% range with the bis-POM prodrug **68** showing the largest decrease. Cyclic 1-(aryl)-1,3-propanyl prodrugs **72**−**78** reduced cholesterol to varying degrees based on the nature of the activating group. While the 3-fluorophenyl prodrug **75** had the largest decrease of all the cyclic 1-(aryl)-1,3-propanyl prodrugs, the 3-bromophenyl prodrug **74** did not achieve any reduction in cholesterol. The 3-chlorophenyl (**72**) and 3-pyridyl (**78**) prodrugs had similar efficacy. Likewise, the diamide prodrugs **79**−**83** showed a large variation in cholesterol lowering as a function of the amino acid. The glycine (**79**) and alanine diamide prodrugs (**80**) had comparable activity, but as the size of the α-substitution of the amino acid increased, a significant decrease in activity was observed, with the phenylalanine diamide prodrug **83** exhibiting no cholesterol reduction.

A representative prodrug from each series was selected for ED_{50} determination in the cholesterol-fed rat assay. Dose responses for prodrugs **68**, **72**, and **79** are presented in Figure 2 with their respective ED_{50} values and maximal pharmacological responses reported in Table 3. Compounds **68** and **72** had similar ED_{50} values (0.4−0.5 mg/kg) and maximal responses, while prodrug **79** appeared slightly more efficacious with an ED_{50} of 0.1 mg/kg and a comparable maximal cholesterol reduction.

Table 3. Cholesterol Lowering Activity at 0.5 mg/kg (po), ED_{50}, and Maximal Cholesterol Decrease in the 24 h Cholesterol-Fed Rat Assay

compd	cholesterol lowering (% decrease)[a]	cholesterol lowering ED_{50}, mg/kg po (max cholesterol decrease)
68	33	0.7 (46%)
69	24	
70	24	
71	20	
72	36	0.48 (55%)
73	28	
74	0	
75	46	
76	29	
77	29	
78	39	
79	42	0.1 (48%)
80	42	
81	23	
82	13	
83	0	

[a] Cholesterol-fed rats were treated by oral gavage with 0.5 mg/kg of the indicated compounds. The percentage change in total plasma cholesterol from pretreatment levels was calculated on a pairwise basis based on the total plasma cholesterol levels measured 24 h after treatment. Data represent mean values ± SEM, $n = 6$.

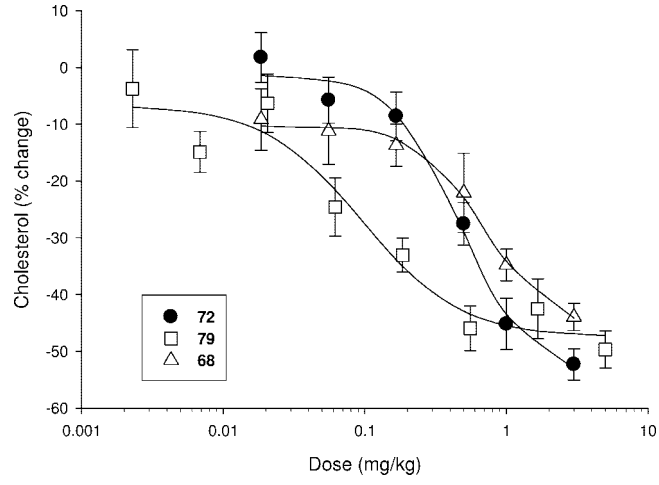


Figure 2. Oral dose-response curves for cholesterol lowering for compounds **68**, **72**, and **79** in the 24 h cholesterol-fed rat assay.

Esterase sensitive prodrugs **68** and **79** were evaluated in human liver S9 for their activation rates and amounts of prodrug remaining after an incubation period of 1 h at 100 μM (Table 4). Prodrug **68** had a cleavage rate twice that of prodrug **79**

Table 4. Rate of Activation and Product Distribution of Esterase Sensitive Prodrugs **68** and **79** in Human Liver S9 after 1 h of Incubation at 100 μM

		% identified metabolite distribution		
compd	rate ((pmol/min)/mg)[a]	compd **22c**	monoacid	prodrug
68	134	11	79	11
79	73	24	6	70

[a] Rate of production of the parent phosphonic acid **22c**.

based on the rate of appearance of parent phosphonic acid **22c**. However, even after 1 h of incubation there was still some prodrug remaining for the very rapidly cleaved bis-POM prodrug **68** (11% remaining) and a much larger amount for the bisamidate prodrug **79** (70% remaining). Since minimization of extrahepatic exposure to prodrug was highly desired, prodrug **72** was selected as the lead compound for further characterization (vide infra).

Pharmacokinetics for Prodrug 72. Pharmacokinetic parameters for prodrug **72** were evaluated in the rat at 3 mg/kg (Table 5). Following oral administration of prodrug **72** the C_{max} and $t_{1/2}$ values of compound **72** were 0.012 $\pm$ 0.008 μg/mL and 0.95 $\pm$ 0.35 h, respectively, while the C_{max} and $t_{1/2}$ values of the parent phosphonic acid **22c** generated were 0.018 $\pm$ 0.003 μg/mL and 9.25 $\pm$ 6.24 h, respectively. After oral administration of prodrug **72**, the plasma AUC_{last} values for the parent compound **22c** were greater (up to ~8-fold) than those for the prodrug **72**, suggesting first pass clearance of **72** by the liver. The oral bioavailability of prodrug **72**, calculated on the basis of plasma AUC of compound **72** following oral vs intravenous administration, was estimated at ~10%. A similar calculation based on plasma levels of phosphonic acid **22c** following oral vs intravenous administration of **72** indicates a relative oral bioavailability of 39%. The lower value for prodrug **72** is an indication of high first-pass clearance.

Discussion

TRs represent an attractive target for lipid control but only if the well-known dose-limiting side effects of TR agonists can be avoided. Recent efforts have focused on eliminating cardiac side effects through development of TRβ_1-selective TR agonists. Compounds **3** and **4** exhibit a 10-fold selectivity for TRβ_1 and a rightward shift in the dose-response curve for various cardiac indices relative to the dose response for cholesterol lowering. These compounds, however, result in decreased weight and a suppression of the hypothalamic−pituitary−thyroid (HPT) axis at lipid lowering doses, suggesting that both are capable of extrahepatic activity. In human clinical trials, the TRβ_1-selective TR agonist **5** is reported to result in significant lipid lowering without affecting the heart. Decreases in both T_4 and T_3 were also noted and possibly due to activation of TRβ_1 in the pituitary.

Our efforts focused on the discovery of PA-based TR agonists with the hope that this approach would selectively activate TRs in the liver while avoiding activation of TRs in extrahepatic tissues. Because of their high negative charge at physiological pH, phosphonic acids usually enter the liver by active transport and are generally associated with very low volumes of distribution.

The binding data demonstrate that phosphonic acids can be excellent ligands for human TRβ_1. Consistent with the observations for carboxylic acid ligands, the substituents on the biaryl system and the length of the side chain have a major impact on the binding affinity. The similar SAR profile for the phosphonic acid series suggests that these compounds may bind to the TR in a similar pattern as the carboxylic acids. However, there are some differences between the analogues based on TR agonist **3** (benzylphenyl series) and those based on TR agonist **4** (diphenyl ether series). While the methyl group is well tolerated at the 3,5-positions in the benzylphenyl series, halogens are the preferred groups at the same positions in the diphenyl ether series. Moreover, the bridging group between the side chain and the phenyl ring has a significant impact on the binding affinity in the benzylphenyl series, as evidenced by the fact that compound **29** (Y = CH_2CH_2, 31.3 nM) was less potent when compared to **22c** (Y = OCH_2, 2.95 nM), while in the diphenyl ether series compound **40** (Y = CH_2CH_2, 2.50 nM) had the same binding potency as compound **57a** (Y = OCH_2, 2.51 nM). The data suggest that the side chains in the two analogue series may have different interactions with the receptor in the vicinity of the phosphonic acid moiety, or the longer carbon−carbon bonds of the methylene bridge between the two phenyl rings (1.54 versus 1.39 Å for C−O) in the benzylphenyl series may have an important effect on the binding of the side chain with TR. Overall, the binding data indicate that compounds with an isopropyl group at the 3′-position, halogen at the 3,5-positions, and a side chain with one or two atoms between the phosphonic acid and the phenyl ring are expected to show optimal potency. Although most phosphonic acid ligands display reduced TR binding affinity when compared with their corresponding carboxylic acids, these compounds offer the opportunity for further studies about the nature of receptor interactions and in vivo activity.

Traditionally, TR ligands are evaluated in a cellular reporter assay to establish functional activity. However, these assays use transfected cultured cell lines that, unlike primary hepatocytes, are unable to effectively transport highly negatively charged phosphonic acids. As such, we evaluated functional activity using an in vivo assay for cholesterol lowering. In addition, to further increase our throughput, we developed a 24 h cholesterol-fed rat assay as a screening tool to evaluate agonism in vivo. While for many species it takes several days of dosing to achieve stable drug-lowered cholesterol levels, in the case of the cholesterol-fed rat, it has been our experience that similar cholesterol reductions are observed following 24 h, 4 days, or 7 days of daily treatment. The screening dose of 0.2 mg/kg was chosen on the basis of the reported ED_{50} for cholesterol lowering in the 7-day model for TR agonists **4** (30 (μg/kg)/day, subcutaneous)[21] and **3** (62 (μg/kg)/day, oral),[20] and we have obtained similar ED_{50} values for **4** and **3** in this assay. While this screening protocol may not have given as much information as a full dose response, it was rapid and sufficient for quickly identifying lead compounds for subsequent evaluation of the lipid lowering dose response relative to various extrahepatic effects.[28] The studies from the 24 h cholesterol-fed rat model further established that phosphonic acid ligands are potent TR agonists in the liver.

On the basis of its cholesterol lowering efficacy, **22c** was chosen for the evaluation of liver-selective TR activity. The mGPDH results demonstrate not only that **22c** and **48** are full agonists in the liver but also that they, unlike their corresponding carboxylic acid analogues, can induce significant TR activity in the liver without showing detectable effects in cardiac tissue. While mGPDH activity may not be directly related to cardiovascular safety, this experiment was designed to test our initial hypothesis that phosphonic acids are much more selective toward hepatic tissues than nonhepatic tissues. The fact that compound **22c** is a full agonist in the liver but does not increase the mGPDH activity in the heart supports our initial hypothesis and suggests that PA TR agonists may result in a greater cardiac

Table 5. Pharmacokinetic Parameters for Compound **72** in Rats

		compd **72**, 3 mg/kg iv[a]		compd **72**, 3 mg/kg po[b]	
parameter	units	compd **72** mean ± SD	compd **22c** mean ± SD	compd **72** mean ± SD	compd **22c** mean ± SD
AUC_{last}	mg·h/L	0.26 ± 0.04	0.34 ± 0.06	0.026 ± 0.011	0.135 ± 0.035
C_{max}[c]	μg/mL	0.60 ± 0.22	0.092 ± 0.017	0.012 ± 0.008	0.018 ± 0.003
T_{max}[c]	h	0.0 ± 0.0	0.60 ± 0.15	2.1 ± 1.0	3.6 ± 1.1
half-life	h	1.23 ± 0.15	8.82 ± 2.38	0.95 ± 0.35	9.25 ± 6.24
MRT[d]	h	1.20 ± 0.20	4.49 ± 0.28	2.49 ± 0.72	7.91 ± 1.60
Cl	(L/h)/kg	11.55 ± 1.93			
V_{ss}	L/kg	14.82 ± 3.99			
MAT[e]	h			1.29 ± 0.72	3.4 ± 1.74
F	%			9.9 ± 4.0	39.2 ± 11.2

[a] The prodrug was dosed in propylene glycol. [b] The prodrug was dosed in PEG-400. [c] Back-extrapolation to *Y*-axis. [d] Mean residence time. [e] Mean absorption time.

TI. These results were further confirmed during the advanced characterization of prodrug **72** where TI values of >125 and >7.5 for cholesterol lowering relative to cardiovascular side effects and TSH suppression, respectively, were observed.[28]

However, as is usually the case with phosphonic acid-based drugs, **22c** has low oral bioavailability and required a prodrug approach to further its development.[28] Fortunately, numerous phosphonate prodrug strategies have been developed to circumvent these limitations, with a few applications leading to clinical drugs (adefovir dipivoxil, tenofovir disoproxil, pradefovir). Therefore, a series of prodrugs, representing the major classes of prodrugs developed to enhance the oral bioavailability of phosphonic acids, was synthesized in one step from phosphonic acid **22c**.

Determination of TR binding affinities for early lead prodrug series established that prodrugs of phosphonic acids are weak ligands (data not shown), as evidenced by the binding affinities for prodrug **72** (TRβ_1 K_i = 14.6 μM and TRα_1 K_i = 12.5 μM).[28] All prodrugs were evaluated orally for efficacy in the 24 h cholesterol-fed rat assay. All esterase-sensitive prodrugs were efficacious in this model with the bis-POM prodrug **68** being significantly better than the others. As previously observed with other parent drugs,[49,57] no correlation was observed between the electronic properties of the activating aryl group of cyclic 1-(aryl)-1,3-propanyl prodrugs and the in vivo results. However, for the diamide prodrugs, there was a good correlation between the in vivo efficacy and the size of the α-substituent on the amino acid. As the size of the substituent increased from methyl to benzyl, the in vivo efficacy decreased (H, Me > $(Me)_2$ > *i*-Pr > Bn). Prodrugs **68**, **72**, and **79** were selected as representative prodrugs of each class for ED_{50} determination. Prodrug **72** was among the most efficacious of the cyclic 1-(aryl)-1,3-propanyl prodrugs tested and was selected on the basis of our experience with the cyclic 1-(3-chlorophenyl)-1,3-propanyl prodrug of the antiviral drug adefovir (pradefovir) and the results generated during its development, including a 48-week phase 2 trial in patients with chronic hepatitis B.[58] All three prodrugs had ED_{50} values below 1 mg/kg, with the diamide prodrug **79** having the lowest.

Prodrugs **68** and **79** require activation by esterases for generation of the parent TR agonist **22c**. Because of the wide distribution of these enzymes in tissues, the fraction of the prodrug not absorbed by the liver after oral administration has the potential to enter extrahepatic tissues if it is not quickly and fully cleaved in the plasma. In contrast, cyclic 1-(aryl)-1,3-propanyl prodrugs are stable in plasma and extrahepatic tissues because of their unique and specific activation mechanism in the liver.[27] Evaluation of esterase-sensitive prodrugs **68** and **79** in esterase-rich human liver S9 still showed the presence of intact prodrug after 1 h of incubation at 100 μM despite good rates of activation for both prodrugs. Concerns over the remaining fraction of esterase-sensitive prodrugs entering the systemic circulation after oral administration, and not being fully activated to prevent their entry into extrahepatic tissues, favored the selection of prodrug **72** as the lead compound. In addition to being stable in extrahepatic tissues, a cyclic 1-(aryl)-1,3-propanyl prodrug has the advantage of selectively generating the parent drug in the liver, further minimizing extrahepatic exposure.[27]

Upon further evaluation of its pharmacokinetic parameters in rats, prodrug **72** was found to have good oral bioavailability and hepatic uptake (rat F = 40%) and was therefore selected as the lead compound for evaluation as a new oral therapy for the treatment of hypercholesterolemia.

Conclusions

A series of phosphonic acid TR agonists has been discovered. The carboxylic acid group of the known TR ligands can be replaced with a phosphonic acid moiety while retaining potent TR binding affinity as well as cholesterol lowering efficacy in the cholesterol-fed rat model. More importantly, the potent full TR agonist **22c** demonstrated selective TR activation in the liver vs heart. On the basis of its binding affinity, cholesterol lowering efficacy, and liver-selective TR agonism, **22c** was chosen for synthesis of a series of prodrugs to circumvent its low oral bioavailability. Potent cholesterol lowering activity, selective liver activation, and good oral bioavailability led to the selection of prodrug **72** for further characterization as a potential drug candidate for the treatment of hypercholesterolemia.

Experimental Section

General Information. All reactions were carried out under a nitrogen atmosphere. NMR spectra were recorded on Varian Gemini-200, Varian Mercury-300, and Varian Mercury-500 spectrometers. Coupling constants (J) and chemical shifts (δ) are expressed in Hz and ppm, respectively. Mass spectra were recorded on a Perkin-Elmer API 2000 spectrometer. All solvents and reagents were purchased from commercial sources and used without further purification. Thin layer chromatography was performed on EM Science silica gel 60 F_{254} plates. Silica gel 60 (230−400 mesh) from EM Science was used when compounds were purified by column chromatography. Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and were not corrected. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ, and NuMega Resonance Laboratories, Inc., San Diego, CA. All protocols involving animal experimentation were reviewed and approved by the Metabasis Therapeutics IACUC (Institution Animal Care and Use Committee) following the guidelines established by the NRC "Guide for the Care and Use of Laboratory Animals".

General Method A. Synthesis of Benzylphenyl Analogues 22a−f. Key intermediates **20a−f** were prepared according to the known method from a variety of MOM-protected phenols **18a−e**

and TIPS-protected aldehydes **17a**,**b**.[39] Alkylation of phenols **20a**−**f** with diethyl tosyloxymethylphosphonate (or diethyl trifluoromethylsulfonyloxymethylphosphonate) in the presence of Cs_2CO_3 at room temperature gave phosphonates **21a**−**f**, which were typically purified by column chromatography on silica gel. Final compounds **22a**−**f** were obtained by deprotection with TMSBr.

[3,5-Dimethyl-4-(4′-hydroxy-3′-isopropylbenzyl)phenoxy]methylphosphonic Acid (22c). To a stirring solution of **18c** (4.50 g, 17.3 mmol) in THF (60 mL) at −78 °C was slowly added a solution of *n*-BuLi (6.90 mL, 17.2 mmol). The reaction mixture was stirred at −78 °C for 50 min, and to it was added a solution of **17a** (4.40 g, 14.4 mmol) in THF (5 mL). The reaction mixture was stirred at −78 °C for 1 h, quenched with saturated aqueous NH_4Cl, and diluted with Et_2O (20 mL). The mixture was allowed to warm to room temperature, and the organic layer was separated. The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with hexanes−ethyl acetate (9:1) to afford **19c** as a colorless oil (6.40 g, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (s, 1 H), 6.94 (m, 2 H), 6.57 (s, 2 H), 6.21 (d, J = 3.2 Hz, 1 H), 5.20 (s, 2 H), 3.48 (s, 3 H), 3.35 (m, 1 H), 2.20 (s, 6 H), 1.10−1.40 (m, 45 H). R_f = 0.42 (hexanes−ethyl acetate, 9:1).

A mixture of **19c** (6.40 g, 13.2 mmol) and Pd−C (0.55 g, 10%) in acetic acid−ethyl acetate (44 mL, 1:9) was stirred under a H_2 atmosphere for 16 h and filtered through a Celite plug. The solvent was removed under reduced pressure, and the residue was dissolved in THF (40 mL). The organic solution was cooled to 0 °C, and to it was added a solution of TBAF (20.0 mL, 20.0 mmol). After 5 min, the reaction mixture was stirred at room temperature for 20 min, quenched with water, and extracted with Et_2O (20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with hexanes−ethyl acetate (1:5) to afford **20c** as a colorless oil (3.50 g, 85%). ^{1}H NMR (300 MHz, CD_3OD): δ 6.90 (m, 2 H), 6.65 (dd, J = 11.2, 3.0 Hz, 1 H), 6.49 (s, 2 H), 5.13 (s, 2 H), 3.88 (s, 2 H), 3.44 (s, 3 H), 3.25 (m, 1 H), 2.13 (s, 6 H), 1.13 (d, J = 6.8 Hz, 6 H); R_f = 0.52 (hexanes−ethyl acetate, 5:1).

To a stirring mixture of NaH (0.85 g, 21.4 mmol) in DMF (40 mL) at 0 °C was added a solution of **20c** (5.60 g, 17.8 mmol) in DMF (7 mL). The reaction mixture was stirred at room temperature for 1 h and cooled to 0 °C. To it was added a solution of diethyl tosyloxymethylphosphonate (6.89 g, 21.4 mmol) in DMF (7 mL). The reaction mixture was stirred at room temperature for 16 h, quenched with MeOH (4 mL) and H_2O (100 mL), and extracted with Et_2O (100 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with hexanes−acetone (3:1) to afford **21c** as a colorless oil (5.32 g, 64%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.94 (d, J = 3.0 Hz, 1 H), 6.87 (d, J = 9.0 Hz, 1 H), 6.73 (s, 2 H), 6.58 (m, 1 H), 5.14 (s, 2 H), 4.36 (d, J = 9.0 Hz, 2 H), 4.10 (m, 4 H), 3.85 (s, 2 H), 3.36 (s, 3 H), 3.21 (m, 1 H), 2.17 (d, J = 6.0 Hz, 6 H), 1.25 (m, 6 H), 1.12−1.10 (d, J = 6.0 Hz, 6 H). R_f = 0.62 (hexanes−acetone, 1:1).

To a solution of **21c** (0.90 g, 1.94 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added TMSBr (3.80 mL, 28.8 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The solvent was removed under reduced pressure, and the residue was treated with CH_3CN−H_2O (1:1, 10 mL). The solvent was removed under reduced pressure, and the residue was treated with toluene (10 mL). The mixture was sonicated for 10 min, filtered, and washed with hexanes to afford **22c** as a pink solid (0.64 g, 91%). ^{1}H NMR (300 MHz, CD_3OD): δ 6.80 (d, J = 1.5 Hz, 1 H), 6.73 (s, 2 H), 6.55 (m, 2 H), 4.18 (d, J = 10.5 Hz, 2 H), 3.87 (s, 2 H), 3.21 (m, 1 H), 2.19 (s, 6 H), 1.12 (d, J = 7.5 Hz, 6 H). ^{13}C NMR (125 MHz, CD_3OD): δ 20.5, 23.0, 28.0, 34.4, 63.4, 64.7, 114.8, 115.8, 126.3, 126.5, 131.9, 132.0, 135.8, 139.4, 153.4, 158.4, 158.5. LC−MS m/z = 365 $[C_{19}H_{25}O_5P + H]^+$. Anal. ($C_{19}H_{25}O_5P \cdot 0.9H_2O$) C, H.

[3,5-Dimethyl-4-(4′-hydroxy-3′-methylbenzyl)phenoxy]methylphosphonic Acid (22a). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.99 (s, 1 H), 6.68−6.525 (m, 5 H), 6.71 (s, 2 H), 4.03 (d, J = 7.5 Hz, 2 H), 3.77 (s, 2 H), 2.15 (s, 6 H), 2.02 (s, 3 H). LC−MS m/z = 335 $[C_{17}H_{21}O_5P - H]$. Anal. ($C_{17}H_{21}O_5P \cdot 0.6H_2O$) C, H.

[3,5-Dimethyl-4-(3′-ethyl-4′-hydroxybenzyl)phenoxy]methylphosphonic Acid (22b). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.96 (s, 1 H), 6.72−6.49 (m, 5 H), 4.03 (d, J = 10.2 Hz, 2 H), 3.78 (s, 2 H), 2.48 (q, J = 8.1 Hz, 2 H), 2.16 (s, 6 H), 1.06 (t, J = 7.5 Hz, 3 H). LC−MS m/z = 349 $[C_{18}H_{23}O_5P - H]$. Anal. ($C_{17}H_{21}O_5P \cdot 1.3H_2O \cdot 0.3CH_2Cl_2$) C, H.

[3,5-Dimethyl-4-(4′-hydroxy-3′-phenylbenzyl)phenoxy]methylphosphonic Acid (22d). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.29 (s, 1 H), 6.60−7.60 (m, 8 H), 4.02 (d, J = 15 Hz, 2 H), 2.18 (s, 2 H). LC−MS m/z = 399 $[C_{29}H_{41}O_{11}P + H]^+$. Anal. ($C_{29}H_{41}O_{11}P \cdot 1.7H_2O \cdot 0.4CH_3OH$) C, H.

[3,5-Dimethyl-4-(3′-*sec*-butyl-4′-hydroxybenzyl)phenoxy]methylphosphonic Acid (22e). ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.92 (s, 1 H), 6.77 (s, 1 H), 6.68 (s, *2* H), 6.61 (d, J = 8.6 Hz, 1 H), 6.47 (d, J = 8.6 Hz, 1 H), 4.02 (d, J = 10.2 Hz, 2 H), 3.78 (s, 2 H), 2.90 (m, 1 H), 1.45 (q, J = 6.6 Hz, 2 H), 1.05 (d, J = 7.0 Hz, 3 H), 0.74 (t, J = 7.0 Hz, 3 H). LC−MS m/z = 379 $[C_{20}H_{27}O_5P + H]^+$. Anal. ($C_{20}H_{27}O_5P \cdot 0.7H_2O$) C, H.

[3,5-Dimethoxy-4-(4′-hydroxy-3′-isopropylbenzyl)phenoxy]methylphosphonic Acid (22f). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.86 (s, 1 H), 6.96 (d, J = 1.8 Hz, 1 H), 6.64 (dd, J = 1.8 Hz, 8.4 Hz, 1 H), 6.54 (d, J = 8.4 Hz, 1 H), 6.27 (s, 2 H), 4.07 (d, J = 10.2 Hz, 2 H), 3.74 (s, 6 H), 3.64 (s, 2 H), 3.08 (m, 1 H), 1.08 (d, J = 6.9 Hz, 6 H). LC−MS m/z = 397 $[C_{19}H_{25}O_7P + H]^+$. Anal. ($C_{19}H_{25}O_7P \cdot 0.4CH_3CO_2C_2H_5 \cdot 0.9H_2O$) C, H.

[3,5-Dimethoxy-4-(4′-hydroxy-3′-isopropylbenzyl)phenoxy]ethylphosphonic Acid (27). To a stirring solution of **20c** (1.00 g, 3.18 mmol) in DMF (30 mL) was added Cs_2CO_3 (5.18 g, 15.9 mmol) followed by 1,2-dibromoethane (1.64 g, 19.1 mmol). The reaction mixture was stirred at 60 °C for 48 h, cooled to room temperature, and diluted with ethyl acetate (10 mL). The mixture was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with hexanes−ethyl acetate (4:1) to afford **25** as an oil (0.26 g, 16%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.94 (m, 2 H), 6.67 (m, 3 H), 5.18 (s, 2 H), 4.32 (m, 2 H), 3.95 (s, 2 H), 3.68 (m, 2 H), 3.51 (s, 3 H), 3.37 (s, 3 H), 3.32 (m, 1 H), 2.26 (s, 6 H), 1.22 (d, J = 6.0 Hz, 6 H). R_f = 0.91 (hexanes−ethyl acetate, 4:1).

A mixture of **25** (0.15 g, 0.36 mmol) and triethyl phosphite (0.18 g, 1.07 mmol) in DMF (2 mL) was heated under reflux for 4 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with hexanes−acetone (1:1) to afford **26** as an oil (0.085 g, 50%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.96 (m, 1 H), 6.89 (m, 1 H), 6.62 (m, 3 H), 5.16 (s, 2 H), 4.12 (m, 2 H), 4.07 (m, 4 H) 3.86 (s, 2 H), 3.37 (s, 3 H), 3.22 (m, 1 H), 2.30 (m, 2 H), 2.17 (s, 6 H), 1.25 (m, 6 H), 1.12 (d, J = 6.0 Hz, 6 H). R_f = 0.10 (hexanes−acetone, 1:1).

Deprotection of **26** with TMSBr as described above afforded **27** as a brown solid (0.05 g, 87%): mp 58−61 °C. LC−MS m/z = 379 $[C_{20}H_{27}O_5P + H]^+$. ^{1}H NMR (300 MHz, CD_3OD): δ 6.84 (s, 1 H), 6.66 (s, 2 H), 6.56 (m, 2 H), 4.26 (m, 2 H), 3.90 (s, 2 H), 3.22 (m, 1 H), 2.30 (m, 1 H), 2.22 (s, 6 H), 1.15 (d, J = 6.0 Hz, 6 H). Anal. ($C_{20}H_{27}O_5P \cdot 0.6H_2O$) C, H.

2-[3,5-Dimethoxy-4-(4′-hydroxy-3′-isopropylbenzyl)phenyl]ethylphosphonic Acid (29). To a solution of **20c** (0.60 g, 1.73 mmol) and DMAP (0.85 g, 6.92 mmol) in CH_2Cl_2 (20 mL) at 0 °C was slowly added Tf_2O (0.44 mL, 2.60 mmol). The reaction mixture was stirred at 0 °C for 2 h and quenched by H_2O (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with hexanes−ethyl acetate (9:1) to afford **23** as a light-yellow oil (0.83 g, 100%). ^{1}H NMR

(300 MHz, DMSO-d_6): δ 7.09 (s, 1 H), 6.87 (s, 2 H), 6.80 (s, 2 H), 5.15 (s, 2 H), 3.84 (s, 6 H), 3.81 (s, 2 H), 3.36 (s, 3 H), 3.20 (m, 1 H), 1.14 (d, J = 6.6 Hz, 6 H). R_f = 0.73 (hexanes−ethyl acetate, 9:1).

A mixture of **23** (0.50 g, 1.73 mmol), Et_3N (0.60 mL, 4.32 mmol), $Pd(PPh_3)_2Cl_2$ (0.08 g, 0.10 mmol), and diethyl vinylphosphonate (0.25 mL, 1.60 mmol) in DMF (3 mL) was heated at 80 °C for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), and washed with aqueous $NaHCO_3$. The organic solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with hexanes−acetone (1:1) to afford **28** as a yellow oil (0.23 g, 45%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, J = 17.4 Hz, 1 H), 7.29 (s, 1 H), 7.11 (m, 2 H), 6.72 (s, 2 H), 6.22 (t, J = 17.1 Hz, 1 H), 5.17 (s, 2 H), 4.21 (m, 4 H), 3.96 (s, 2 H), 3.87 (s, 6 H), 3.49 (s, 3 H), 3.31 (m, 1 H), 1.40 (t, J = 6.9 Hz, 6 H), 1.23 (d, J = 6.6 Hz, 6 H). R_f = 0.40 (hexanes−acetone, 1:1).

A mixture of **28** (0.10 g, 0.2 mmol) and Pd−C (0.02 g, 10%) in MeOH (20 mL) was stirred under a H_2 atmosphere at room temperature for 16 h and filtered through a Celite plug. The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (5 mL). Deprotection with TMSBr as described above afforded **29** as a pink foam in 91% yield. ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.88 (s, 1 H), 7.01 (d, J = 1.8 Hz, 1 H), 6.71 (dd, J = 1.8 Hz, J = 8.0 Hz, 1 H), 6.55 (d, J = 8.4 Hz, 1 H), 6.5 (s, 2 H), 3.76 (s, 6 H), 3.69 (s, 2 H), 3.08 (m, 1 H), 2.72 (m, 2 H), 1.82 (m, 2 H), 1.08 (d, J = 7.0 Hz, 6 H). LC−MS m/z = 395 $[C_{20}H_{27}O_6P + H]^+$. Anal. ($C_{20}H_{27}O_6P \cdot 1.3H_2O$) C, H.

[4-(4′-Hydroxy-3′-isopropylbenzyl)-3,5-dimethylphenylamino]methylphosphonic Acid (32). A solution of **23** (2.04 g, 4.57 mmol), Et_3N (1.27 mL, 9.14 mmol), 1,3-bis(diphenylphosphino)propane (0.19 mL, 0.45 mmol), MeOH (3.71 mL, 91.4 mmol), and $Pd(OAc)_2$ (0.10 g, 0.46 mmol) in DMF (25 mL) was heated at 90 °C under a CO atmosphere (60 psi) in a Parr bomb for 16 h. The reaction mixture was cooled to 0 °C, diluted with ethyl acetate (25 mL), and washed with H_2O. The organic solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with hexanes−ethyl acetate (4:1) to afford **24** as an oil (1.52 g, 93%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.68 (s, 2 H), 6.97 (m, 1 H), 6.91 (m, 2 H), 6.20 (m, 1 H), 5.16 (s, 2 H), 4.01 (s, 3 H), 3.85 (s, 3 H), 3.21 (m, 1 H), 2.28 (s, 6 H), 1.14 (d, J = 6.0 Hz, 6 H). TLC conditions: R_f = 0.42 (hexanes−ethyl acetate, 4:1).

To a stirring solution of **24** (0.75 g, 2.11 mmol) in MeOH (20 mL) at 0 °C was added 1 N NaOH (12.6 mL, 12.6 mmol). The reaction mixture was heated at 50 °C for 16 h, cooled to 0 °C, and acidified with 2 N HCl. The mixture was extracted with ethyl acetate (20 mL) and washed with H_2O. The organic solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired acid as a white solid (0.71 g, 98%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.76 (s, 1 H), 7.65 (s, 2 H), 6.98 (m, 1 H), 6.91 (m, 1 H), 6.60 (m, 1 H), 5.17 (s, 2 H), 4.00 (s, 2 H), 3.37 (s, 3 H), 3.23 (m, 1 H), 2.27 (s, 6 H), 1.14 (d, J = 6.0 Hz, 6 H).

To a solution of the above acid (0.70 g, 2.04 mmol), *tert*-butanol (0.75 g, 10.22 mmol), and Et_3N (0.71 g, 5.11 mmol) in toluene (30 mL) was added diphenylphosphoryl azide (0.44 mL, 2.04 mmol). The reaction mixture was heated under reflux for 16 h, cooled to room temperature, and poured into a cold solution of 0.25 N HCl (30 mL). The mixture was extracted with ethyl acetate (20 mL) and washed with H_2O. The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with hexanes−ethyl acetate (9:1) to afford **30** as a yellow oil (0.63 g, 75%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.16 (s, 1 H), 7.16 (s, 2 H), 6.96 (m, 1 H), 6.90 (m, 1 H), 6.62 (m, 1 H), 5.16 (s, 2 H), 3.86 (s, 2 H), 3.37 (s, 3 H), 3.22 (m, 1 H), 2.15 (s, 6 H), 1.48 (m, 9 H), 1.23 (d, J = 6.0 Hz, 6 H). R_f = 0.72 (hexanes−ethyl acetate, 7:3).

To a mixture of **30** (0.315 g, 0.76 mmol) in THF (8 mL) at −78 °C was added a solution of LDA (0.46 g, 0. 91 mmol). The reaction mixture was stirred at −78 °C for 20 min, and diethyl trifluoromethylsulfonyloxymethylphosphonate (0.16 g, 0.76 mmol) was added. The reaction mixture was stirred at −78 °C for 1 h, allowed to warm to room temperature, and stirred for 4 h. The reaction was quenched with aqueous NH_4Cl and extracted with ethyl acetate (10 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with hexanes−ethyl acetate (1:1) to afford **31** as an oil (0.21 g, 49%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.00 (s, 2 H), 6.94 (m, 1 H), 6.90 (m, 1 H), 6.64 (m, 1 H), 5.16 (s, 2 H), 4.09 (d, J = 6.0 Hz, 2 H), 4.00 (m, 4 H), 3.8 (m, 2 H), 3.37 (s, 3 H), 3.22 (m, 1 H), 2.20 (s, 6 H), 1.40 (s, 9 H), 1.27 (m, 6 H), 1.13 (m, 6 H). R_f = 0.20 (hexanes−ethyl acetate, 2:3).

To a stirring solution of **31** (0.19 g, 0.34 mmol) in MeOH (4 mL) at 0 °C was added 2 N HCl (1.68 mL, 3.37 mmol). The reaction mixture was stirred at room temperature for 48 h, cooled to 0 °C, neutralized with $NaHCO_3$, and extracted with ethyl acetate (20 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with hexanes−ethyl acetate (2:3) to afford the desired phosphonate as a white solid (0.07 g, 51%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.95 (s, 1 H), 6.84 (m, 1 H), 6.63 (m, 1 H), 6.50 (m, 1 H), 6.45 (s, 2 H), 5.39 (m, 1H), 4.06 (s, 6 H), 3.74 (s, 2 H), 3.51 (m, 2 H), 3.13 (m, 1 H), 2.09 (s, 6 H), 1.20 (m, 6 H), 1.11 (d, J = 6.0 Hz, 6 H). R_f = 0.29 (hexanes−ethyl acetate, 4:1).

Deprotection of **31** with TMSBr as described above afforded **32** as an off-white powder in 79% yield: mp 147−150 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.97 (s, 1 H), 6.86 (m, 1 H), 6.59 (m, 1 H), 6.49 (m, 1 H), 6.45 (s, 2 H), 3.74 (s, 2 H), 3.20 (d, J = 12.0 Hz, 2 H), 3.13 (m, 1 H), 2.10 (s, 6 H), 1.12 (d, J = 6.0 Hz, 6 H). LC−MS m/z = 364 $[C_{19}H_{26}NO_4P - H]^+$. Anal. ($C_{19}H_{26}NO_4P \cdot 1.0H_2O \cdot 0.2HBr \cdot 0.2CH_3CO_2CH_2CH_3$) C, H, N, Br.

General Method B. Synthesis of Diphenyl Ether Analogues 38a−c. Key intermediates **35a−c** were prepared from the iodonium salt **33** and commercially available methyl benzoates **34a−c** according to the known method.[16] Reduction of **35a−c** with DIBAL-H followed by treatment of the resulting benzyl alcohols with CBr_4 and PPh_3 gave benzyl bromides **36a−c**, which underwent Michaelis−Arbuzov reaction with triethyl phosphite to provide phosphonates **37a−c**. Final compounds **38a−c** were obtained by deprotection with TMSBr and BBr_3.

[3,5-Dichloro-4-(4′-hydroxy-3′-isopropylphenoxy)]benzylphosphonic Acid (38b). To a mixture of **33** (4.55 g, 8.88 mmol) and copper powder (0.88 g, 13.8 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added a solution of Et_3N (1.06 mL, 3.71 mmol) and **34b** (1.65 g, 6.90 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at room temperature for 72 h and filtered through a Celite plug. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with hexanes−acetone (6:1) to afford **35b** as a solid (2.02 g, 80%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.10 (m, 1 H), 6.85 (m, 2 H), 6.50 (m, 1 H), 3.90 (s, 3 H), 3.76 (s, 3 H), 3.21 (m, 1 H), 1.14 (d, J = 6.0 Hz, 6 H). R_f = 0.51 (hexanes−acetone, 6:1).

To a mixture of **35b** (1.40 g, 3.37 mmol) in THF (10 mL) at 0 °C was added a solution of DIBAL-H (8.12 mL, 8.12 mmol). The reaction mixture was stirred at room temperature for 16 h, quenched with cold 1 N HCl, and extracted with ethyl acetate (15 mL). The organic layer was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the benzyl alcohol as an off-white solid (0.94 g, 100%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.54 (s, 2 H), 6.81 (m, 2 H), 6.40 (m, 1 H), 5.51 (m, 1 H), 4.54 (d, J = 6.0 Hz, 2 H), 3.75 (s, 3 H), 3.21 (m, 1 H), 1.13 (d, J = 6.0 Hz, 6 H). R_f = 0.27 (hexanes−acetone, 6:1).

To a stirred solution of PPh_3 (0.42 g, 1.61 mmol) and CBr_4 (0.534 g, 1.61 mmol) in Et_2O (15 mL) at room temperature was added the above benzyl alcohol (0.50 g, 1.46 mmol). The reaction mixture was stirred at room temperature for 16 h, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with hexanes−acetone (9:1)

to afford **36b** as a solid (0.32 g, 54%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.77 (s, 2 H), 6.82 (m, 2 H), 6.38 (m, 1 H), 4.75 (s, 2 H), 3.75 (s, 3 H), 3.22 (m, 1 H), 1.13 (d, J = 6.0 Hz, 6 H). R_f = 0.46 (hexanes−acetone, 4:1).

A mixture of **36b** (0.61 g, 1.51 mmol) and triethyl phosphite (0.61 g, 3.56 mmol) in DMF (2 mL) was heated under reflux for 4 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with H_2O. The organic layer was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with hexanes−acetone (7:3) to afford **37b** as an oil (0.59 g, 85%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.55 (s, 2 H), 6.88 (d, J = 9.0 Hz, 1 H), 6.75 (d, J = 3.0 Hz, 1 H), 6.43 (m, 1 H), 4.01 (m, 4 H), 3.75 (s, 3 H), 3.41 (m, 2 H), 3.22 (m, 1 H), 1.20 (m, 6 H), 1.12 (d, J = 6.0 Hz, 6 H). R_f = 0.22 (hexanes−acetone, 4:1).

To a solution of **37b** (0.59 g, 1.28 mmol) in CH_2Cl_2 (10 mL) at −30 °C was added TMSBr (2.53 mL, 19.2 mmol). The reaction mixture was stirred at room temperature for 16 h, and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (25 mL) and cooled to −78 °C. To it was added a solution of BBr_3 (19.0 mL, 19.0 mmol). The reaction mixture was stirred at −78 °C for 10 min, allowed to warm to room temperature, and stirred for 16 h. The mixture was poured into ice and extracted with ethyl acetate (10 mL). The organic layer was washed with H_2O, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure to afford **38b** as a brown solid (0.20 g, 40%): mp 178−181 °C. LC−MS m/z = 391 [$C_{16}H_{17}Cl_2O_5P$ − H]$^-$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.08 (s, 1 H), 7.48 (s, 2 H), 6.72 (m, 2 H), 6.25 (m, 1 H), 3.18 (m, 1 H), 3.00 (d, J = 21.0 Hz, 2 H), 3.11 (m, 1 H), 1.14 (d, J = 6.0 Hz, 6 H). Anal. ($C_{16}H_{17}Cl_2O_5P\cdot 0.2CH_3CO_2CH_2CH_3\cdot 0.5H_2O$) C, H.

[3,5-Dimethyl-4-(4′-hydroxy-3′-isopropylphenoxy)]benzylphosphonic Acid (38a). Mp 79−82 °C. LC−MS m/z = 351 [$C_{18}H_{23}O_5P$ + H]$^+$. ^{1}H NMR (300 MHz, CD_3OD): δ 6.93 (s, 2 H), 6.51 (m, 2 H), 6.13 (m, 1 H), 3.13 (m, 1 H), 2.98 (d, J = 21.0 Hz, 2 H), 1.96 (s, 6 H), 1.04 (d, J = 6.0 Hz, 6 H). Anal. ($C_{18}H_{23}O_5P\cdot 1.2H_2O$) C, H.

[3,5-Dibromo-4-(4′-hydroxy-3′-isopropylphenoxy)]benzylphosphonic Acid (38c). Mp 145 °C. LC−MS m/z = 536 [$C_{20}H_{25}Br_2O_5P$ + H]$^+$. ^{1}H NMR (300 MHz, CD_3OD): δ 7.53 (s, 2 H), 6.50 (m, 2 H), 6.23 (m, 1 H), 3.98 (m, 4 H), 3.11 (m, 1 H), 1.21 (m, 6 H), 1.02 (d, J = 6.0 Hz, 6 H). Anal. ($C_{20}H_{25}Br_2O_5P$) C, H.

2-[3,5-Dibromo-4-(4′-hydroxy-3′-isopropylphenoxy)phenyl]ethylphosphonic Acid (40). To a solution of dimethyl methylphosphonate (0.06 g, 0.48 mmol) in THF (3 mL) at −78 °C was slowly added a solution of LDA (0.25 mL, 0.50 mmol). After 30 min, a solution of **36c** (0.20 g, 0.40 mmol) in THF was added. The reaction mixture was stirred at −78 °C for 5 min, allowed to warm to room temperature, and stirred for 2 h. The reaction mixture was quenched with aqueous NH_4Cl (10 mL) and extracted with Et_2O (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with hexanes−acetone (1:1) to afford **39** (0.09 g, 43%) as a colorless oil: ^{1}H NMR (300 MHz, CD_3OD): δ 7.64 (s, 2 H), 6.82 (d, J = 10.0 Hz, 1 H), 6.75 (d, J = 4.2 Hz, 1H), 6.44 (dd, J = 2.8, 10.2 Hz, 1 H), 3.79 (d, J = 2.8 Hz, 6 H), 3.76 (s, 3 H), 3.30 (m, 1 H), 2.94 (m, 2 H), 2.23 (m, 2 H), 1.17 (d, J = 7.0 Hz, 6 H). LC−MS m/z = 537 [$C_{20}H_{25}$ Br_2O_5P + H]$^+$. R_f = 0.50 (hexanes−acetone, 1:1).

Deprotection of **39** with TMSBr and BBr_3 as described above gave **40** as an off-white solid: mp 56−59 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.02 (s, 1 H), 7.65 (s, 2 H), 6.64 (m, 2 H), 6.21 (dd, J = 2.8, 10.2 Hz, 1 H), 3.14 (m, 1 H), 2.79 (m, 2 H), 1.87 (m, 2 H), 1.11 (d, J = 7.0 Hz, 6 H). LC−MS m/z = 495 [$C_{17}H_{19}$ Br_2O_5P + H]$^+$. Anal. ($C_{17}H_{19}$ $Br_2O_5P\cdot 0.5H_2O$) C, H.

3,5-Diiodo-4-(4′-hydroxy-3′-isopropylphenoxy)benzylphosphonic Acid (45). A mixture of **41** (1.0 g, 4.40 mmol) and triethyl phosphite (1.0 mL, 5.80 mmol) in DMF (2.8 mL) was heated at 155 °C for 4 h. The reaction mixture was cooled to room temperature, quenched with H_2O (10 mL), and extracted with ethyl acetate (20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with hexanes−acetone (3:2) to afford the phosphonate as a colorless oil. The desired product was dissolved in MeOH (12 mL), and to it was added Pd−C (10%, 0.33 g). The mixture was stirred under a H_2 atmosphere for 16 h, filtered through a Celite plug, and concentrated under reduced pressure to afford **42** as an oil (0.9 g, 84%). ^{1}H NMR (300 MHz, CD_3OD): δ 7.12 (d, J = 8.4 Hz, 2 H), 6.73 (d, J = 8.4 Hz, 2 H), 4.05 (m, 4 H), 3.16 (s, 1 H), 3.09 (s, 1 H), 1.26 (t, J = 6.9 Hz, 6 H). LC−MS m/z = 245 [$C_{11}H_{17}O_4P$ + H]$^+$. R_f = 0.50 (hexanes−acetone, 1:1).

To a solution of **42** (0.50 g, 2.05 mmol) in CH_2Cl_2 (12 mL) at room temperature was added bis(pyridine)iodonium tetrafluoroborate (1.67 g, 4.50 mmol). The reaction mixture was stirred at room temperature for 1 h, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with hexanes−acetone (1:1) to afford **43** as a white solid (0.92 g, 90%). ^{1}H NMR (300 MHz, CD_3OD): δ 7.67 (d, J = 2.7 Hz, 2 H), 4.05 (m, 4 H), 3.10 (d, J = 12.9 Hz, 2 H), 1.28 (t, J = 6.9 Hz, 6 H). LC−MS m/z = 497 [$C_{11}H_{16}I_2O_4P$ + H]$^+$. R_f = 0.57 (hexanes−acetone, 1:1).

Coupling of **43** with **33** as described above gave **44** as a colorless oil in 85% yield. ^{1}H NMR (300 MHz, CD_3OD): δ 7.87 (d, J = 2.7 Hz, 2 H), 6.80 (d, J = 6.7 Hz, 2 H), 6.65 (s, 1 H), 6.40 (dd, J = 2.7 Hz, 6.9 Hz, 2 H), 4.09 (m, 4 H), 3.78 (s, 3 H), 3.24 (d, J = 12.9 Hz, 2 H), 3.20 (m, 1 H), 1.28 (t, J = 6.9 Hz, 6 H), 1.13 (d, J = 6.8 Hz, 6 H). LC−MS m/z = 497 [$C_{11}H_{16}I_2O_4P$ + H]$^+$. R_f = 0.90 (hexanes−acetone, 1:1).

Deprotection of **44** with TMSBr and BBr_3 as described above afforded **45** as a white solid in 92% yield. ^{1}H NMR (300 MHz, CD_3OD): δ 7.85 (d, J = 2.4 Hz, 2 H), 6.59 (m, 2 H), 6.28 (dd, J = 2.4, 8.7 Hz, 1 H), 3.22 (m, 1 H), 3.18 (s, 1 H), 3.08 (s, 1 H), 1.18 (d, J = 6.9 Hz, 6 H). LC−MS m/z = 575 [$C_{16}H_{17}I_2O_4P$ + H]$^+$. Anal. ($C_{16}H_{17}I_2O_5P\cdot 0.3$ $H_2O\cdot 0.5CH_3OH$) C, H, I.

3,5-Diiodo-4-(4′-hydroxy-3′-iodophenoxy)benzylphosphonic Acid (48). To a mixture of **43** (0.40 g, 0.81 mmol), 4-(*tert*-butyldimethylsiloxy)phenylboronic acid (0.61 g, 2.42 mmol), $Cu(OAc)_2$ (0.18 g, 0.99 mmol), and 4 Å molecular sieves (1.20 g) in CH_2Cl_2 (7 mL) was added a solution of pyridine (0.4 mL, 4.8 mmol) and Et_3N (0.7 mL, 4.8 mmol). The reaction mixture was stirred at room temperature for 48 h, filtered through a Celite plug, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with hexanes−acetone (3:1) to afford the desired product as a white solid. The resulting product was dissolved in THF (3 mL) and cooled to 0 °C. To it was added a solution of TBAF (0.30 mL, 0.30 mmol), and the reaction mixture was stirred at room temperature for 20 min. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel, eluting with hexanes−acetone (1:1) to afford **46** as a white solid (0.06 g, 13%). ^{1}H NMR (300 MHz, CD_3OD): δ 7.84 (s, 2 H), 6.70 (d, J = 8.4 Hz, 2 H), 6.56 (d, J = 8.4 Hz, 2 H), 4.15 (m, 4 H), 3.25 (d, J = 12.8 Hz, 2 H), 1.30 (m, 6 H). LC−MS m/z = 589 [$C_{17}H_{19}I_2O_5P$ + H]$^+$. R_f = 0.40 (hexanes−acetone, 1:1).

To a solution of **46** (0.10 g, 0.17mmol) in EtOH (4 mL) at 0 °C was added 40% aqueous $MeNH_2$ (0.40 mL) followed by a solution of KI (0.16 g, 0.51 mmol) and I_2 (0.06 g, 0.23 mmol) in H_2O (0.5 mL). The reaction mixture was stirred at 0 °C for 1 h, quenched with H_2O, and extracted with ethyl acetate (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with MeOH−CH_2Cl_2 (1:19) to afford **47** as a yellow solid (0.10 g, 69%). ^{1}H NMR (300 MHz, CD_3OD): δ 7.85 (s, 2 H), 7.00 (d, J = 5.2 Hz, 1 H), 6.74 (d, J = 8.4 Hz, 1 H), 6.64 (dd, J = 3.2, 8.4 Hz, 1 H), 4.18 (m, 5 H), 3.08 (m, 1 H), 2.78 (m, 1 H), 1.36 (m, 6 H). LC−MS m/z = 715 [$C_{17}H_{18}I_3O_5P$ + H]$^+$. R_f = 0.55 (MeOH-CH_2Cl_2, 1:19).

Deprotection of **47** with TMSBr as described above gave **48** as a white solid in 90%. ^{1}H NMR (300 MHz, CD_3OD): δ 7.86 (d, J = 2.4 Hz, 2 H), 6.99 (d, J = 6.4 Hz, 1 H), 6.74 (d, J = 8.7 Hz, 1 H), 6.62 (dd, J = 2.4, 8.7 Hz, 1 H), 3.15 (s, 1 H), 3.08 (s, 1 H).

LC−MS m/z=659 $[C_{13}H_{10}I_3O_5P+H]^+$. Anal. ($C_{13}H_{10}I_3O_5P\cdot 1.6H_2O\cdot 0.5CH_3OH$) C, H, I.

General Method C. Synthesis of Compounds with an Oxygen-Linked Side Chain 57a−c. Compounds **57a−c** were prepared by selective alkylation of the key intermediates **55a−c** with diethyl trifluoromethylsulfonyloxymethylphosphonate followed by deprotection with TMSBr. Phenols **55a−c** were synthesized from compounds **49** and **51** with different methods.

[3,5-Diiodo-4-(4′-hydroxy-3′-isopropylphenoxy)phenoxy]methylphosphonic Acid (57b). To a solution of **51** (0.2 g, 0.93 mmol) in CH_2Cl_2 (9.3 mL) at 0 °C was added bis(pyridine)iodonium tetrafluoroborate (0.76 g, 2.06 mmol). The reaction mixture was stirred at room temperature for 1 h, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with hexanes−acetone (9:1) to afford **52b** as an off-white solid (0.22 g, 50%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.60 (s, 1 H), 8.06 (m, 2 H), 7.72 (s, 2 H), 7.59 (m, 3 H). R_f = 0.45 (hexanes−acetone, 4:1).

To a mixture of **33** (0.77 g, 1.51 mmol) and Cu powder (0.13 g, 2.01 mmol) in CH_2Cl_2 (4.4 mL) at 0 °C was added a solution of **52b** (0.47 g, 1.00 mmol) and Et_3N (0.15 mL, 1.10 mmol) in CH_2Cl_2 (4 mL). The reaction mixture was stirred at room temperature for 24 h and filtered through a Celite plug. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with hexanes−acetone (9:1) to afford **53b** as an off-white solid (0.61 g, 98%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.10 (m, 2 H), 7.96 (s, 2 H), 7.73 (m, 1 H), 7.60 (m, 2 H), 6.85 (d, J = 9.0 Hz, 1 H), 6.73 (d, J = 3.0 Hz, 1 H), 6.35 (m, 1 H), 3.74 (s, 3 H), 3.21 (m, 1 H), 1.13 (d, J = 6.0 Hz, 6 H). R_f = 0.42 (hexanes−acetone, 9:1).

A mixture of **53b** (0.10 g, 0.16 mmol) and 1 N NaOH (0.81 mL, 0.81 mmol) in MeOH (1.63 mL) was stirred at room temperature for 24 h. The reaction mixture was neutralized with 2 N HCl, diluted with H_2O, and extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were concentrated under reduced pressure and the crude product was purified by preparatory TLC with hexanes−acetone (4:1) as mobile phase to afford **54b** as an off-white solid (0.08 g, 95%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.99 (s, 1 H), 7.28 (s, 2 H), 6.81 (d, J = 12.0 Hz, 1 H), 6.67 (d, J = 3.0 Hz, 1 H), 6.30 (m, 1 H), 3.72 (s, 3 H), 3.18 (m, 1 H), 1.11 (d, J = 6.9 Hz, 6 H). R_f = 0.42 (hexanes−acetone, 7:3).

To a stirred solution of **54b** (0.28 g, 0.55 mmol) in CH_2Cl_2 (17 mL) at −78 °C was added BBr_3 (13.1 mL, 13.1 mmol, 1 M solution in CH_2Cl_2). The reaction mixture was stirred at −78 °C for 10 min, allowed to warm to room temperature, and stirred for 16 h. The reaction mixture was poured into ice and extracted with CH_2Cl_2 (20 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with hexanes−acetone (7:3) to afford **55b** as an off-white solid (0.18 g, 66%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.95 (s, 1 H), 8.91 (s, 1 H), 7.27 (s, 2 H), 6.62 (d, J = 9.0 Hz, 1 H), 6.56 (d, J = 3.0 Hz, 1 H), 6.18 (m, 1 H), 3.72 (s, 3 H), 3.14 (m, 1 H), 1.10 (d, J = 6.0 Hz, 6 H). R_f = 0.28 (hexanes−acetone, 7:3).

To a mixture of **55b** (0.07 g, 0.14 mmol) and Cs_2CO_3 (0.22 g, 0.67 mmol) in DMF (1.35 mL) at 0 °C was added diethyl trifluoromethylsulfonyloxymethylphosphonate (0.04 g, 0.14 mmol). The reaction mixture was stirred at room temperature for 5 h, quenched with 1 N HCl, and extracted with ethyl acetate (10 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparatory TLC with hexanes−acetone (3:2) as mobile phase to afford **56b** as an off-white solid (0.048 g, 55%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.95 (s, 1 H), 7.57 (s, 2 H), 6.63 (d, J = 9.0 Hz, 1 H), 6.56 (d, J = 3.0 Hz, 1 H), 6.19 (m, 1 H), 4.51 (d, J = 9.0 Hz, 2 H), 4.08 (m, 4 H), 3.14 (m, 1 H), 1.25 (m, 6 H), 1.10 (d, J = 6.0 Hz, 6 H). R_f = 0.29 (hexanes−acetone, 3:2).

Deprotection of **56b** with TMSBr as described above afforded **57b** as an off-white solid in 63% yield: mp 180 °C, dec. LC−MS m/z = 589 $[C_{16}H_{17}I_2O_6P - H]^-$. LC−MS m/z = 589 $[C_{16}H_{17}I_2O_6P - H]^-$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.95 (s, 1 H), 7.51 (s, 2 H), 6.63 (d, J = 9.0 Hz, 1 H), 6.57 (d, J = 3.0 Hz, 1 H), 6.18 (m, 1 H), 4.10 (d, J = 9.0 Hz, 2 H), 1.10 (d, J = 6.0 Hz, 6 H). LC−MS m/z = 589 $[C_{16}H_{17}I_2O_6P - H]^-$ Anal. ($C_{16}H_{17}I_2O_6P\cdot 0.4H_2O$) C, H.

[3,5-Dibromo-4-(4′-hydroxy-3′-isopropylphenoxy)phenoxy]methylphosphonic Acid (57a). Mp 77−80 °C. LC−MS m/z = 495 $[C_{16}H_{17}Br_2O_6P - H]^-$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.99 (s, 1 H), 7.42 (s, 2 H), 6.63 (m, 2 H), 6.22 (m, 1 H), 4.21 (d, J = 9.0 Hz, 2 H), 3.11 (m, 1 H), 1.10 (d, J = 6.0 Hz, 6 H). Anal. ($C_{16}H_{17}Br_2O_6P\cdot 0.2C_6H_{14}$) C, H.

[3,5-Dimethyl-4-(4′-hydroxy-3′-isopropylphenoxy)phenoxy]methylphosphonic Acid (57c). Mp 60−64 °C. LC−MS m/z = 367 $[C_{18}H_{23}O_6P + H]^+$. ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.88 (s, 1 H), 6.76 (s, 2 H), 6.60 (m, 2 H), 6.17 (m, 1 H), 4.04 (d, J = 15.0 Hz, 2 H), 3.13 (m, 1 H), 2.01 (s, 6 H), 1.10 (d, J = 6.0 Hz, 6 H). Anal. ($C_{18}H_{23}O_6P\cdot 0.7H_2O$) C, H.

3,5-Dimethyl-4-(4′-hydroxy-3′-isopropylphenoxy)phenol (55c). To a mixture of **33** (4.80 g, 9.38 mmol) and Cu powder (0.79 g, 12.5 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added a solution of **49** (0.94 g, 6.26 mmol) and Et_3N (0.96 mL, 6.89 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred at room temperature for 72 h and filtered through a Celite plug. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with hexanes−acetone (19:1) to afford **50** as an oil (2.00 g, 100%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.96 (s, 1 H), 7.75 (s, 2 H), 6.85 (m, 1 H), 6.73 (m, 1 H), 6.36 (m, 1 H), 3.74 (s, 3 H), 3.19 (m, 1 H), 2.15 (s, 6 H), 1.12 (d, J = 6.0 Hz, 6 H). R_f = 0.51 (hexanes−acetone, 17:3).

To a solution of **50** (0.18 g, 0.60 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added *m*-chloroperoxybenzoic acid (0.22 g, 0.905 mmol). The reaction mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate (10 mL). The organic solution was washed with saturated $NaHCO_3$ (10 mL) and concentrated under reduced pressure. To the residue was added MeOH (5 mL) and 1 N NaOH (1.81 mL, 1.81 mmol). The reaction mixture was stirred at room temperature for 4 h, acidified with 2 N HCl, extracted with ethyl acetate (10 mL), and washed with H_2O. The organic solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparatory TLC with hexanes−acetone (4:1) as mobile phase to afford **54c** as an oil (0.08 g, 47%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.17 (s, 1 H), 6.82 (m, 1 H), 6.70 (m, 1 H), 6.51 (s, 2 H), 6.32 (m, 1 H), 3.71 (s, 3 H), 3.18 (m, 1 H), 1.95 (s, 6 H), 1.12 (d, J = 6.0 Hz, 6 H). R_f = 0.44 (hexanes−acetone, 4:1).

General Method D. Synthesis of Compounds with a Nitrogen-Linked Side Chain 61a,b. The final compounds were prepared from commercially available anilines **58a**,**b** by Boc protection followed by coupling with the iodonium salt **33**, *N*-alkylation and deprotection with TMSBr and BBr_3.

[3,5-Dichloro-4-(4′-hydroxy-3′-isopropylphenoxy)phenylamino]methylphosphonic Acid (61a). To a solution of **58a** (4.0 g, 22.5 mmol) in THF (25 mL) was added di-*tert*-butyl dicarbonate (5.88 g, 27.0 mmol). The reaction mixture was heated under reflux for 2.5 h, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with hexanes−acetone (9:1) to afford the desired Boc-protected aniline as an off-white solid (5.80 g, 93%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.70 (s, 1 H), 9.44 (s, 1 H), 7.46 (s, 2 H), 1.48 (s, 9 H). R_f = 0.39 (hexanes−acetone, 7:3).

To a mixture of **33** (2.76 g, 5.39 mmol) and Cu powder (0.46 g, 7.18 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added a solution of Et_3N (0.55 mL, 3.95 mmol) and the above phenol (1.00 g, 3.59 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 14 h and filtered through a Celite plug. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with hexanes−acetone (7:3) to afford **59a** as an off-white solid (1.45 g, 95%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.81 (s, 1 H), 7.68 (m, 2 H), 6.79 (m, 2 H), 6.42 (m, 1 H), 3.75 (s, 3 H), 3.20 (m, 1 H), 1.51 (s, 9 H), 1.33 (d, J = 6.0 Hz, 6 H). R_f = 0.64 (hexanes−acetone, 7:3).

To a mixture of **59a** (0.40 g, 0.94 mmol) in THF (12 mL) at 0 °C was added NaH (0.06 g, 1.22 mmol, 60% dispersion in oil). The reaction mixture was stirred at room temperature for 1 h and cooled to 0 °C. To the stirring mixture was added diethyl trifluoromethylsulfonyloxymethylphosphonate (0.18 g, 0.94 mmol). The reaction mixture was stirred at room temperature for 2 h, quenched with H_2O, and extracted with ethyl acetate (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with hexanes−ethyl acetate (3:2) to afford **60a** as an oil (0.34 g, 63%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.64 (s, 2 H), 6.90 (m, 1 H), 6.76 (s, 1 H), 6.45 (m, 1 H), 4.95 (d, J = 9.0 Hz, 2 H), 4.01 (m, 4 H), 3.76 (s, 3 H), 3.21 (m, 1 H), 1.43 (s, 9 H), 1.20 (m, 6 H), 1.13 (d, J = 6.0 Hz, 6 H). R_f = 0.15 (hexanes−ethyl acetate, 3:2).

Deprotection of **60a** with TMSBr and BBr_3 as described above afforded **61a** as an off-white solid in 85% yield: mp 97−100 °C. LC−MS m/z = 405,407 $[C_{16}H_{18}Cl_2NO_5P + H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.02 (s, 2 H), 6.90 (m, 2 H), 6.71 (m, 2 H), 6.32 (m, 2 H), 3.36 (m, 2 H), 3.21 (m, 1 H), 1.17 (d, J = 6.0 Hz, 6 H). Anal. ($C_{16}H_{18}Cl_2NO_5P \cdot 0.1CH_3CO_2CH_2CH_3 \cdot 0.3H_2O$) C, H, N.

[3,5-Dibromo-4-(4′-hydroxy-3′-isopropylphenoxy)phenylamino]methylphosphonic Acid (61b). ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.95 (m, 1 H), 7.02 (s, 2 H), 6.63 (m, 2 H), 6.23 (m, 1 H), 3.31 (d, J = 12.0 Hz, 2 H), 3.14 (m, 1 H), 1.12 (d, J = 6.0 Hz, 6 H). LC−MS m/z = 496 $[C_{16}H_{18}Br_2NO_5P - H]^+$. Anal. ($C_{16}H_{18}Br_2NO_5P \cdot 0.7CH_3COCH_3 \cdot 0.7H_2O$) C, H, N.

2,6-Dimethyl-4-methylsulfanylphenoxytriisopropylsilane (63). To a stirring solution of **62** (0.5 g, 1.4 mmol) in THF (15 mL) at −78 °C was added *n*-BuLi (2.5 M in hexanes, 0.56 mL). The reaction mixture was stirred at −78 °C for 1 h, and to it was added methyldisulfanylmethane (0.16 mL, 1.82 mmol). The reaction mixture was allowed to warm to room temperature, stirred for 1 h, quenched with saturated NH_4Cl, and extracted with Et_2O (8 mL). The organic solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford **63** as an oil (0.46 g, 100%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.92 (s, 2 H), 2.41 (s, 3 H), 2.20 (s, 6 H), 1.29 (m, 3 H), 1.10 (d, J = 7.2 Hz, 18 H). R_f = 0.57 (hexanes−ethyl acetate, 49:1).

Diethyl (3,5-Dimethyl-4-triisopropylsilanyloxyphenylsulfanyl)methylphosphonate (64). To a stirring solution of **63** (2.18 g, 6.72 mmol) in CCl_4 (25 mL) at room temperature was added NCS (0.99 g, 7.39 mmol). The reaction mixture was stirred at room temperature for 16 h and filtered through a Celite plug. The solvent was removed under reduced pressure to afford crude product as a colorless oil (2.4 g, 100%). The crude product was dissolved in triethyl phosphite (1.5 mL) and heated at 180 °C for 30 min in a microwave oven. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with hexanes−ethyl acetate (1:1) to afford **64** as a yellow oil (1.6 g, 52%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.09 (s, 2 H), 4.98 (m, 4 H), 3.31 (d, J = 13.8 Hz, 2 H), 2.17 (s, 6 H), 1.25 (m, 9 H), 1.09 (d, J = 7.0 Hz, 18 H). R_f = 0.45 (hexanes−ethyl acetate, 3:2).

Diethyl (4-Hydroxy-3,5-dimethylphenylsulfanylmethyl)phosphonate (65). To a stirring solution of **64** (1.6 g, 3.47 mmol) in THF (20 mL) at room temperature was added a solution of TBAF (5.2 mL, 1 M in THF). The reaction mixture was stirred at room temperature for 2 h, and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (20 mL) and washed with H_2O. The organic solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with hexanes−ethyl acetate (5:1) to afford **65** as a yellow oil (0.90 g, 85%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.41 (s, 1 H), 7.06 (s, 2 H), 3.98 (m, 4 H), 3.22 (d, J = 13.6 Hz, 2 H), 2.12 (s, 6 H), 1.22 (d, J = 7.2 Hz, 6 H). R_f = 0.44 (hexanes−ethyl acetate, 4:1).

Diethyl [4-(4′-Methoxy-3′-isopropylphenoxy)-3,5-dimethylphenylsulfanylmethyl]phosphonate (66). To a stirring mixture of **33** (0.35 g, 0.68 mmol) and Cu powder (0.05 g, 0.79 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added a solution of **65** (0.16 g, 0.53 mmol) and Et_3N (0.08 mL, 0.58 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature for 16 h and filtered through a Celite plug. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel, eluting with hexanes−ethyl acetate (2:1) to afford **66** as a yellow oil (0.14 g, 60%). ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.24 (s, 2 H), 6.79 (d, J = 8.8 Hz, 1 H), 6.72 (d, J = 3.0 Hz, 1 H), 6.32 (dd, J = 3.0, 8.8 Hz, 1 H), 4.02 (m, 4 H), 3.73 (s, 3 H), 3.45 (d, J = 14.4 Hz, 2 H), 3.18 (m,1 H), 2.04 (s, 6 H), 1.15 (m, 12 H). R_f = 0.51 (hexanes−ethyl acetate, 2:1).

[4-(4′-Hydroxy-3′-isopropylphenoxy)-3,5-dimethylphenylsulfanylmethyl]phosphonic Acid (67). Deprotection of **66** with TMSBr and BBr_3 as described above gave **67** in 51% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.91 (s, 1 H), 7.16 (s, 2 H), 6.64 (m, 2 H), 6.21 (dd, J = 3.3, 8.7 Hz, 1 H), 4.13 (m, 3 H), 2.02 (s, 6 H), 1.11 (d, J = 6.9 Hz, 6 H). LC−MS m/z = 383 $[C_{18}H_{23}O_5PS + H]^+$. Anal. ($C_{18}H_{23}O_5PS \cdot 0.15CF_3COOH \cdot 0.2CH_3CH_2OCH_2CH_3$) C, H.

Diethyl *N*-[3,5-Dimethyl-4-(3′-isopropyl-4′-methoxyphenoxy)]-carbamonylphosphonate (15). A mixture of **14**[16] (0.1 g, 0.35 mmol) and diphosgene (0.04 g, 0.19 mmol) in dioxane (3 mL) was heated at 60 °C for 3 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. To the residue was added a solution of diethyl phosphite (0.06 g, 0.42 mmol) in hexanes (1 mL) with 3 drops of Et_3N. The reaction mixture was heated under reflux for 3 h and cooled to room temperature. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel, eluting with hexanes−ethyl acetate (3:1) to afford **15** as an oil (0.10 g, 64%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44 (s, 1 H), 7.17 (s, 2 H), 6.10−6.60 (m, 3 H), 4.10 (m, 4 H), 3.58 (s, 3 H), 3.07 (m, 1 H), 1.92 (s, 3 H), 1.93 (s, 3 H), 1.22 (m, 6 H), 0.99 (m, 6 H). LC−MS m/z = 450 $[C_{23}H_{32}NO_6P + H]^+$. R_f = 0.30 (hexanes−ethyl acetate, 3:1).

***N*-[3,5-Dimethyl-4-(3′-isopropyl-4′-methoxyphenoxy)]carbamonylphosphonic Acid (16).** Deprotection of **15** with TMSBr and BBr_3 as described above afforded **16** as a yellow solid in 42% yield. ^{1}H NMR (300 MHz, CD_3OD): δ 7.39 (s, 2 H), 6.60 (m, 2 H), 6.26 (m, 1 H), 3.23 (m, 1 H), 2.09 (s, 6 H), 1.14 (d, J = 5.1 Hz, 6 H). LC−MS m/z = 380 $[C_{18}H_{22}NO_6P + H]^+$. Anal. ($C_{18}H_{22}NO_6P \cdot 0.2H_2O \cdot 0.3CH_3OH$) C, H, N.

Diethyl 2-(4-Benzyloxyphenyl)-1-hydroxyiminoethylphosphonate (7). To a solution of **6** (4.0 g, 16.2 mmol) in THF (10 mL) at room temperature was slowly added triethyl phosphite (3.33 mL, 19.5 mmol). The reaction mixture was stirred at room temperature for 16 h, and the solvent was removed under reduced pressure. The residue was treated with hexanes (20 mL) and filtered. The solid was dissolved in pyridine (25 mL), and to it was added hydroxylamine hydrochloride (1.96 g, 28 mmol). The reaction mixture was stirred at room temperature for 72 h, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with hexanes−ethyl acetate (7:3) to afford **7** as a colorless oil (5.2 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18−7.38 (m, 7 H), 6.80 (d, J = 6.2 Hz, 2 H), 4.94 (s, 2 H), 3.80−4.10 (m, 4 H), 3.80 (s, 1 H), 3.76 (s, 1 H), 1.16 (t, J = 6.0 Hz, 6 H). LC−MS m/z = $[C_{23}H_{32}NO_6P + H]^+$. R_f = 0.55 (hexanes−ethyl acetate, 3:2).

2-(4-Benzyloxyphenyl) 1-*tert*-Butoxycarbonylaminoethylphosphonate (8). To a mixture of **7** (2.0 g, 5.3 mmol) and $NiCl_2$ (2.53 g, 10.6 mmol) in MeOH (40 mL) at room temperature was slowly added $NaBH_4$ (1.0 g, 26.4 mmol). The reaction mixture was stirred at room temperature for 16 h, and the solvent was removed under reduced pressure. The residue was treated with 10% aqueous KOH (100 mL) and extracted with Et_2O (2 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in THF (14 mL), and to it was added $(BOC)_2O$ (0.74 g, 3.4 mmol). The reaction mixture was heated under reflux for 4 h and cooled to room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with MeOH−CH_2Cl_2 (1:19) to afford **8** as colorless oil (1.12

g, 46%). ^{1}H NMR (300 MHz, CD_3OD): δ 7.38 (m, 5 H), 7.13 (d, J = 8.4 Hz, 2 H), 6.88 (d, J = 8.4 Hz, 2 H), 4.88 (s, 2 H), 4.12 (m, 5 H), 3.08 (m, 1 H), 2.70 (m, 1 H), 1.34 (m, 6 H). LC−MS m/z = 464 $[C_{24}H_{34}NO_6P + H]^+$. R_f = 0.45 (MeOH−CH_2Cl_2, 1:19).

Diethyl 1-*tert*-Butoxycarbonylamino-2-(3,5-diiodo-4-hydroxyphenyl)ethylphosphonate (9). A mixture of **8** (1.1 g, 2.4 mmol) and Pd−C (0.23 g, 10%) in MeOH (10 mL) was stirred under a H_2 atmosphere for 16 h and filtered through a Celite plug. The solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$ (15 mL). To it was added bis(pyridine)iodonium tetrafluoroborate (1.90 g, 5.1 mmol). The reaction mixture was stirred at room temperature for 1 h, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with hexanes−acetone (1:1) to afford **9** as a yellow solid (1.30 g, 88%). ^{1}H NMR (300 MHz, CD_3OD): δ 7.67 (s, 2 H), 7.13 (d, J = 8.4 Hz, 1 H), 4.00−4.25 (m, 5 H), 3.00 (m, 1 H), 2.64 (m, 1 H), 1.38 (m, 6 H). LC−MS m/z = 626 $[C_{17}H_{26}I_2NO_6P + H]^+$. R_f = 0.70 (hexanes−acetone, 1:1).

Diethyl 1-*tert*-Butoxycarbonylamino-2-[4-(4′-*tert*-butyldimethylsilanyloxy)phenoxy-3,5-diiodophenyl]ethylphosphonate (10). To a mixture of **9** (0.6 g, 0.96 mmol), 4-(*tert*-butyldimethylsiloxy)phenylboronic acid (0.73 g, 2.89 mmol), $Cu(OAc)_2$ (0.21 g, 1.16 mmol), and 4 Å molecular sieves (1.20 g) in CH_2Cl_2 (8 mL) was added a solution of pyridine (0.40 mL) and Et_3N (0.70 mL). The reaction mixture was stirred at room temperature for 48 h, filtered through a Celite plug, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with hexanes−acetone (3:1) to afford **10** as a white solid (0.48 g, 60%). ^{1}H NMR (300 MHz, CD_3OD): δ 7.64 (s, 2 H), 7.18 (d, J = 8.4 Hz, 1 H), 6.64 (d, J = 8.4 Hz, 1 H), 6.53 (d, J = 8.4 Hz, 1 H), 6.38 (d, J = 8.4 Hz, 1 H), 4.00 (m, 5 H), 2.90 (m, 1 H), 2.58 (m, 1 H), 1.20 (m, 6 H), 0.90 (m, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H). LC−MS m/z = 832 $[C_{29}H_{44}I_2NO_7PSi + H]^+$. R_f = 0.60 (hexanes−acetone, 7:3).

Diethyl 1-*tert*-Butoxycarbonylamino-2-[4-(4′-hydroxyphenoxy)-3,5-diiodophenyl]ethylphosphonate (11). To a mixture of **10** (0.45 g, 0.54 mmol) in THF (6 mL) at 0 °C was added a solution of TBAF (0.81 mL, 0.81 mmol, 1 M in THF). The reaction mixture was stirred at room temperature for 20 min, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with hexanes−acetone (1:1) to afford **11** as a white solid (0.24 g, 62%). ^{1}H NMR (300 MHz, CD_3OD): δ 7.74 (s, 2 H), 6.58 (d, J = 8.4 Hz, 2 H), 6.45 (d, J = 8.4 Hz, 2 H), 4.12 (m, 5 H), 3.08 (m, 1 H), 2.64 (m, 1 H), 1.32 (m, 6 H). LC−MS m/z = 618 $[C_{18}H_{22}I_2NO_5P + H]^+$. R_f = 0.40 (hexanes−acetone, 1:1).

Diethyl 1-Amino-2-[3,5-diiodo-4-(4′-hydroxy-3-iodophenoxy)phenyl]ethylphosphonate (12). A mixture of **11** (0.14 g, 0.20 mmol) in 70% aqueous TFA (5 mL) was stirred at room temperature for 1 h, and the solvent was removed under reduced pressure. The residue was dissolved in EtOH (4 mL) and cooled to 0 °C. To it was added 40% aqueous $MeNH_2$ (0.80 mL) followed by a solution of KI (0.16 g, 0.96 mmol) and I_2 (0.06 g, 0.23 mmol) in H_2O (0.6 mL). The reaction mixture was stirred at 0 °C for 1 h, quenched with H_2O, and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with MeOH−CH_2Cl_2 (1:24) to afford **12** as a yellow solid (0.10 g, 69%). ^{1}H NMR (300 MHz, CD_3OD): δ 7.85 (s, 2 H), 7.00 (d, J = 5.2 Hz, 1 H), 6.74 (d, J = 8.4 Hz, 1 H), 6.64 (dd, J = 3.2, 8.4 Hz, 1 H), 4.18 (m, 5 H), 3.08 (m, 1 H), 2.78 (m, 1 H), 1.36 (m, 6 H). R_f = 0.55 (MeOH−CH_2Cl_2, 1:24).

1-Amino-2-[3,5-diiodo-4-(4′-hydroxy-3′-iodophenoxy)]phenylethylphosphonic Acid (13). Deprotection of **12** with TMSBr as described above afforded **13** as a yellow solid in 95% yield. ^{1}H NMR (300 MHz, CD_3OD): δ 7.91 (s, 2 H), 7.02 (d, J = 2.7 Hz, 1 H), 6.74 (d, J = 8.4 Hz, 2 H), 6.64 (dd, J = 3.0, 8.4 Hz, 1 H), 3.60 (m, 1 H), 2.92 (m, 1 H). LC−MS m/z = 688 $[C_{14}H_{13}I_3NO_5P + H]^+$. Anal. ($C_{14}H_{13}I_3NO_5P \cdot 1.0H_2O \cdot 0.3HBr$) C, H, N.

General Procedure for the Synthesis of Acyloxymethyl or Alkoxycarbonyloxymethyl Prodrugs of Phosphonic Acid 22c: Di(pivaloyloxymethyl) [3,5-Dimethyl-4-(4′-hydroxy-3′-isopropylbenzyl)phenoxy]methylphosphonate (68). To a mixture of **22c** (0.2 g, 0.5 mmol) and *N*,*N*-diisopropylethylamine (0.57 mL, 3.0 mmol) in CH_3CN (5 mL) at 0 °C was added pivaloyloxymethyl iodide[48] (0.6 mL, 3.0 mmol). The reaction mixture was stirred at room temperature for 16 h, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with acetone−hexanes (1:3) to afford **68** as a white solid (0.22 g, 76%). ^{1}H NMR (300 MHz, CD_3OD): δ 6.82 (d, J = 2.1 Hz, 1H), 6.71 (s, 2H), 6.59 (d, J = 7.8 Hz, 1H), 6.54 (dd, J = 7.8, 2.1 Hz, 1H), 5.85−5.70 (m, 4H), 4.46 (d, J = 9.9 Hz, 2H), 3.90 (s, 2H), 3.22 (hpt, J = 6.9 Hz, 1H), 2.22 (s, 6H), 1.22 (s, 18H), 1.14 (d, J = 6.9 Hz, 6H). LC−MS m/z = 593 $[C_{31}H_{45}O_9P + H]^+$. Anal. ($C_{31}H_{45}O_9P \cdot 0.3H_2O$) C, H.

Di(ethoxycarbonyloxymethyl) [3,5-Dimethyl-4-(4′-hydroxy-3′-isopropylbenzyl)phenoxy]methylphosphonate (69). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.01 (s, 1H), 6.86 (d, J = 2.1 Hz, 1H), 6.73 (s, 2H), 6.62 (d, J = 8.1 Hz, 1H), 6.46 (dd, J = 8.1, 2.1 Hz, 1H), 5.72 (s, 2H), 5.68 (s, 2H), 4.49 (d, J = 7.5 Hz, 2H), 4.16 (q, J = 6.9 Hz, 4H), 3.82 (s, 2H), 3.14 (hpt, J = 6.9 Hz, 1H), 2.18 (s, 6H), 1.20 (t, J = 6.9 Hz, 6H), 1.11 (d, J = 6.9 Hz, 6H). LC−MS m/z = 569 $[C_{27}H_{37}O_{11}P + H]^+$. Anal. ($C_{27}H_{37}O_{11}P$) C, H.

Di(isopropoxycarbonyloxymethyl) [3,5-Dimethyl-4-(4′-hydroxy-3′-isopropylbenzyl)phenoxy]methylphosphonate (70). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.06 (s, 1H), 6.86 (d, J = 2.1 Hz, 1H), 6.73 (s, 2H), 6.62 (d, J = 7.8 Hz, 1H), 6.45 (dd, J = 7.8, 2.1 Hz, 1H), 5.71 (s, 2H), 5.67 (s, 2H), 4.80 (hpt, J = 6.1 Hz, 2H), 4.48 (d, J = 9.9 Hz, 2H), 3.82 (s, 2H), 3.14 (hpt, J = 6.9 Hz, 1H), 2.18 (s, 6H), 1.23 (d, J = 6.9 Hz, 6H), 1.21 (d, J = 6.9 Hz, 6H), 1.11 (d, J = 6.9 Hz, 6H). LC−MS m/z = 597 $[C_{29}H_{41}O_{11}P + H]^+$. Anal. ($C_{29}H_{41}O_{11}P$) C, H.

Di-(*S*-acetyl-2-thioethyl) [3,5-Dimethyl-4-(4′-hydroxy-3′-isopropylbenzyl)phenoxy]methylphosphonate (71). A mixture of *S*-acetyl-2-thioethanol (0.12 g, 0.96 mmol), **22c** (0.10 g, 0.25 mmol), pyridine (1 mL), and dicyclohexylcarbodiimide (0.14 g, 0.69 mmol) in DMF (2.5 mL) was heated at 70 °C for 16 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate−hexanes (1:1) to afford **71** as an oil (0.09 g, 56%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.98 (s, 1H), 6.84 (d, J = 1.8 Hz, 1H), 6.73 (s, 2H), 6.61 (d, J = 8.4 Hz, 1H), 6.44 (dd, J = 8.4, 1.8 Hz, 1H), 4.42 (d, J = 9.9 Hz, 2H), 4.16−4.11 (m, 4 H), 3.80 (s, 2H), 3.17−3.10 (m, 5H), 2.34 (s, 6H), 2.17 (s, 6H), 1.09 (d, J = 6.9 Hz, 6H). LC−MS m/z = 569 $[C_{27}H_{37}O_7PS_2 + H]^+$. Anal. ($C_{27}H_{37}O_7PS_2$) C, H.

General Procedure for the Synthesis of Cis Cyclic 1-Aryl-1,3-propanyl Prodrugs of Phosphonic Acid 22c: (2*R*,4*S*)-2-[(3,5-Dimethyl-4-(4′-hydroxy-3′-isopropylbenzyl)-phenoxy)methyl]-4-(3-chlorophenyl)-2-oxido[1,3,2]dioxaphosphonane (72). To a mixture of **22c** (0.2 g, 0.55 mmol), (*S*)-1-(3-chlorophenyl)-1,3-propane diol (0.31 g, 1.6 mmol), and pyridine (1 mL) in DMF (5 mL) at room temperature was added 1,3-dicyclohexylcarbodiimide (0.34 g, 1.6 mmol). The reaction mixture was heated at 70 °C for 4 h, cooled to room temperature, and filtered through a Celite plug. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel, eluting with CH_2Cl_2−MeOH (96:4) to afford the cis-prodrug **72** (0.06 g, 15%) as a white solid: mp 77−82 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.97 (s, 1H), 7.47 (m, 1H), 7.38−7.31 (m, 3H), 6.82 (d, J = 2.1 Hz, 1H), 6.73 (s, 2H), 6.59 (d, J = 8.1 Hz, 1H), 6.43 (dd, J = 8.1, 2.0 Hz, 1H), 5.73 (ddd, J = 9.8, 3.7, 1.2 Hz, 1H), 4.61−4.50 (m, 1H), 4.45 (d, J = 9.0 Hz, 2H), 4.45−4.35 (m, 1H), 3.78 (s, 2H), 3.08 (hpt, J = 9.0 Hz, 1H), 2.30−2.10 (m, 2H), 2.14 (s, 6H), 1.07 (d, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 142.9 (d, J = 6.9 Hz), 156.2 (d, J = 13.3 Hz), 152.7, 138.3, 134.3, 133.7, 131.2, 130.8, 130.2, 128.7, 126.0, 125.9, 125.3, 124.8, 115.2, 114.3, 78.4 (d, J = 7.2 Hz), 66.9 (d, J = 7.5 Hz), 61.7 (d, J = 169.0 Hz), 33.6, 33.3 (d, J = 6.6 Hz), 26.9, 22.9, 20.5. ^{32}P NMR (121 MHz,

DMSO-d_6): δ 29.5. LC−MS m/z = 516 $[C_{28}H_{32}ClO_5P + H]^+$. Anal. ($C_{28}H_{32}ClO_5P \cdot 0.2H_2O$) C, H.

***cis*-2-[(3,5-Dimethyl-4-(4′-hydroxy-3′-isopropylbenzyl)phenoxy)-methyl]-4-(4-chlorophenyl)-2-oxido[1,3,2]dioxaphosphonane (73).** Yellow solid, mp 77−80 °C. ^{1}H NMR (300 MHz, CD_3OD): δ 7.37−7.28 (m, 4H), 6.82 (d, J = 1.8 Hz, 1H), 6.71 (s, 2H), 6.58 (d, J = 8.4 Hz, 1H), 6.53 (dd, J = 8.1, 1.8 Hz, 1H), 5.72 (br d, J = 11.1 Hz, 1H), 4.75−4.63 (m, 1H), 4.59−4.42 (m, 3H), 3.90 (s, 2H), 3.20 (hpt, J = 6.8 Hz, 1H), 2.50−2.30 (m, 2H), 2.20 (s, 6H), 1.12 (d, J = 6.8 Hz, 6H). ^{31}P NMR (121.5 MHz, CD_3OD) δ 18.45. LC−MS m/z = 515 $[C_{28}H_{32}ClO_5P + H]^+$. Anal. ($C_{28}H_{32}ClO_5P \cdot 0.1H_2O \cdot 0.1CH_2Cl_2$) C, H.

***cis*-2-[(3,5-Dimethyl-4-(4′-hydroxy-3′-isopropylbenzyl)phenoxy)-methyl]-4-(3-bromophenyl)-2-oxido[1,3,2]dioxaphosphonane (74).** Yield 80 mg (21%), mp 70−75 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.98 (s, 1H), 7.63 (s, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.40−7.28 (m, 2H), 6.84 (s, 1H), 6.75 (s, 2H), 6.60 (d, J = 9.0 Hz, 1H), 6.45 (d, J = 9.0 Hz, 1H), 5.74 (br d, J = 12.0 Hz, 1H), 4.65−4.55 (m, 1H), 4.55−4.38 (m, 3H), 3.81 (s, 2H), 3.12 (hpt, J = 6.9 Hz, 1H), 2.30−2.10 (m, 2H), 2.16 (s, 6 H), 1.09 (d, J = 6.9 Hz, 6 H). ^{31}P NMR (121.5 MHz, CD_3OD) δ 15.45. LC−MS m/z = 559, 561 $[C_{28}H_{32}BrO_5P + H]^+$. Anal. ($C_{28}H_{32}BrO_5P$) C, H.

***cis*-2-[(3,5-Dimethyl-4-(4′-hydroxy-3′-isopropylbenzyl)phenoxy)-methyl]-4-(3-fluorophenyl)-2-oxido[1,3,2]dioxaphosphonane (75).** Yield 130 mg (38%), mp 75−80 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.98 (s, 1H), 7.41−7.36 (m, 1H), 7.24−7.14 (m, 3H), 6.83 (s, 1H), 6.74 (s, 2H), 6.60 (d, J = 8.1 Hz, 1H), 6.45 (d, J = 8.1 Hz, 1H), 5.75 (br d, J = 10.8 Hz, 1H), 4.60−4.50 (m, 1H), 4.50−4.41 (m, 3H), 3.80 (s, 2H), 3.12 (hpt, J = 6.9 Hz, 1H), 2.27−2.29 (m, 1H), 2.16 (s, 6H), 1.09 (d, J = 6.9 Hz, 6H). LC−MS m/z = 499 $[C_{28}H_{32}FO_5P + H]^+$. Anal. ($C_{28}H_{32}FO_5P \cdot 0.2EtOAc$) C, H.

***cis*-2-[(3,5-Dimethyl-4-(4′-hydroxy-3′-isopropylbenzyl)phenoxy)methyl]-4-(3,5-dichlorophenyl)-2-oxido[1,3,2]dioxaphosphonane (76).** Yield 50%, mp 79−81 °C. ^{1}H NMR (300 MHz, CD_3OD): δ 7.44 (s, 2H), 6.84 (d, J = 1.8 Hz, 1H), 6.76 (s, 2H), 6.61 (d, J = 8.4 Hz, 1H), 6.55 (dd, J = 8.4, 1.8 Hz, 1H), 5.77 (br d, J = 10.5 Hz, 1H), 4.80−4.65 (m, 1H), 4.63−4.55 (m, 1H), 4.54 (d, J = 9.3 Hz, 2H), 3.93 (s, 2H), 3.23 (hpt, J = 6.8 Hz, 1H), 2.50−2.30 (m, 2H), 2.24 (s, 6H), 1.15 (d, J = 6.8 Hz, 6H). ^{31}P NMR (121.5 MHz, CD_3OD) δ 16.78. LC−MS m/z = 549 $[C_{28}H_{31}Cl_2O_5P + H]^+$. Anal. ($C_{28}H_{31}Cl_2O_5P \cdot 0.1H_2O$) C, H, Cl.

***cis*-2-[(3,5-Dimethyl-4-(4′-hydroxy-3′-isopropylbenzyl)phenoxy)-methyl]-4-(pyrid-4-yl)-2-oxido[1,3,2]dioxaphosphonane (77).** Yield 20%, mp 75−77 °C. ^{1}H NMR (300 MHz, CD_3OD): δ 8.55−8.50 (m, 2H), 7.50−7.43 (m, 2H), 6.85 (d, J = 1.8 Hz, 1H), 6.72 (s, 2H), 6.61 (d, J = 8.4 Hz, 1H), 6.54 (dd, J = 8.4, 1.8 Hz, 1H), 5.90−5.80 (m, 1H), 4.83−4.50 (m, 3H), 3.93 (s, 2H), 3.23 (hpt, J = 6.8 Hz, 1H), 2.50−2.30 (m, 2H), 2.23 (s, 6H), 1.15 (d, J = 6.8 Hz, 6H). ^{31}P NMR (121.5 MHz, CD_3OD) δ 17.29. LC−MS m/z = 482 $[C_{27}H_{32}NO_5P + H]^+$. Anal. ($C_{27}H_{32}NO_5P$) C, H, N.

***cis*-2-[(3,5-Dimethyl-4-(4′-hydroxy-3′-isopropylbenzyl)phenoxy)-methyl]-4-(pyrid-3-yl)-2-oxido[1,3,2]dioxaphosphonane (78).** Yield 108 mg (50%), mp 75−78 °C. ^{1}H NMR (300 MHz, CD_3OD): δ 8.67 (s, 1H), 8.60−8.50 (m, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.50−7.38 (m, 1H), 6.86 (d, J = 1.8 Hz, 1H), 6.75 (s, 2H), 6.62 (d, J = 8.4 Hz, 1H), 6.53 (dd, J = 8.4, 1.8 Hz, 1H), 5.88 (br d, J = 11.4 Hz, 1H), 4.83−4.50 (m, 3H), 3.93 (s, 2H), 3.23 (hpt, J = 6.8 Hz, 1H), 2.60−2.42 (m, 1H), 2.35−2.20 (m, 1H), 2.23 (s, 6H), 1.15 (d, J = 6.8 Hz, 6H). ^{31}P NMR (121.5 MHz, CD_3OD) δ 17.17. LC−MS m/z = 482 $[C_{27}H_{32}NO_5P + H]^+$. Anal. ($C_{27}H_{32}NO_5P$) C, H, N.

General Procedure for the Synthesis of Bis-amidate Prodrugs of Phosphonic Acid 22c: Di-*N*-(ethoxycarbonylmethylamino) [3,5-Dimethyl-4-(4′-hydroxy-3′-isopropylbenzyl)phenoxy]methylphosphonic Diamide (79). To a stirred solution of **22c** (0.41 g, 1.11 mmol) and DMF (0.1 mL, 1.11 mmol) in dichloromethane (5.6 mL) at 0 °C was added oxalyl chloride (0.38 mL, 4.4 mmol). The reaction mixture was heated at reflux for 3 h, cooled to room temperature, and concentrated under reduced pressure. To the residue at 0 °C was added a solution of L-alanine ethyl ester (0.57 g, 4.3 mmol) and *N*,*N*-diisopropylethylamine (0.6 mL, 4.3 mmol) in CH_2Cl_2. The reaction mixture was stirred for 14 h at room temperature and concentrated under reduced pressure. The residue was partitioned between EtOAc (50 mL) and aqueous $NaHCO_3$ solution (100 mL). The organic layer was separated, washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluting with CH_2Cl_2−MeOH (95:5) to give **79** as an off-white foam (41.3 mg, 20%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.97 (s, 1H), 6.81 (s, 1H), 6.63 (s, 2H), 6.57 (d, J = 8.4 Hz, 1H), 6.43 (d, J = 7.8 Hz, 1 H), 4.82−4.70 (m, 2H), 4.15−4.00 (m, 2H), 4.00 (d, J = 6.6 Hz, 2H), 3.78 (s, 2H), 3.75−3.58 (m, 4H), 3.11 (hpt, J = 6.9 Hz, 1H), 2.15 (s, 6H), 1.16 (t, J = 7.2 Hz, 6H), 1.07 (d, J = 6.6 Hz, 6H). ^{31}P NMR (121.5 MHz, DMSO-d_6) δ 21.36. LC−MS m/z = 535.3 $[C_{27}H_{39}N_2O_7P + H]^+$. Anal. ($C_{27}H_{39}N_2O_7P$). C, H, N.

Di-*N*-(L-1-ethoxycarbonylethylamino) [3,5-Dimethyl-4-(4′-hydroxy-3′-isopropylbenzyl)phenoxy]methylphosphonamide (80). Yellow solid (175 mg, 52%), mp 48−50 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (s, 1H), 6.95 (s, 1H), 6.66 (s, 2H), 6.64 (d, J = 8.4 Hz, 1H), 6.55 (d, J = 7.8 Hz, 1 H), 5.10 (s, 1H), 4.30−4.1 (m, 6H), 3.93 (s, 2H), 3.45 (q, J = 9.3 Hz, 2H), 3.20 (hpt, J = 6.9 Hz, 1H), 2.24 (s, 6H), 1.46 (d, J = 7.2 Hz, 6H), 1.28 (t, J = 7.5 Hz, 6H), 1.24 (d, J = 6.9 Hz, 6H). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 96.08. LC−MS m/z = 563 $[C_{29}H_{43}N_2O_7P + H]^+$. Anal. ($C_{29}H_{43}N_2O_7P \cdot 0.5H_2O$) C, H, N.

Di-*N*-(1-ethoxycarbonyl-1-methylethylamino)[3,5-dimethyl-4-(4′-hydroxy-3′-isopropylbenzyl)]phenoxy]methylphosphonamide (81). ^{1}H NMR (300 MHz, CD_3OD): δ 6.85 (s, 1H), 6.75 (s, 2H), 6.61 (d, J = 8.4 Hz, 1H), 6.54 (dd, J = 8.4, 1.8 Hz, 1H), 4.25−4.15 (m, 6H), 4.00 (d, J = 6.6 Hz, 2H), 3.93 (s, 2H), 3.12 (hpt, J = 6.9 Hz, 1H), 2.24 (s, 6H), 1.61 (s, 3H), 1.56 (s, 3H), 1.30 (t, J = 7.1 Hz, 6H), 1.16 (d, J = 6.6 Hz, 6H). ^{31}P NMR (121.5 MHz, CD_3OD) δ 92.88. LC−MS m/z = 591 $[C_{31}H_{47}N_2O_7P + H]^+$. Anal. ($C_{31}H_{47}N_2O_7P$) C, H, N.

Di-*N*-(L-1-ethoxycarbonyl-2-methylpropylamino) [3,5-Dimethyl-4-(3′-isopropyl-4′-hydroxybenzyl)phenoxy]methylphosphonamide (82). Mp 52−55 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (s, 2H), 6.84 (d, J = 1.8 Hz, 1H), 6.55 (s, 2H), 6.52 (d, J = 7.2 Hz, 1H), 6.42 (dd, J = 7.2, 1.8 Hz, 1H), 5.10 (b s, 1H), 4.20−4.02 (m, 6H), 3.80 (s, 2 H), 3.35−3.22 (m, 1H), 3.20−3.08 (s, 1H), 3.11 (hpt, J = 6.9 Hz, 1H), 2.13 (s, 6H), 2.15−2.00 (m, 2H), 1.20−1.09 (m, 12H), 0.95 (t, J = 6.9 Hz, 6H), 0.81 (t, J = 6.9 Hz, 6H). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 95.11. LC−MS m/z = 619 $[C_{33}H_{51}N_2O_7P + H]^+$. Anal. ($C_{33}H_{51}N_2O_7P \cdot 0.75H_2O$) C, H, N.

Di-*N*-(L-1-ethoxycarbonyl-2-phenylethylamino) [3,5-Dimethyl-4-(4′-hydroxy-3′-isopropylbenzyl)phenoxy]methylphosphonamide (83). Mp 60−63 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.00 (s, 1H), 7.30−7.15 (m, 10H), 6.84 (s, 1H), 6.63 ((d, J = 8.1 Hz, 1H), 6.53 (s, 2H), 6.52 (dd, J = 8.1, 1.8 Hz, 1H), 4.75 (t, 1H), 4.38 (t, 1H), 4.10−3.90 (m, 6H), 3.95 (s, 2H), 3.63 (d, J = 9.0 Hz, 2H), 3.15 (hpt, J = 6.9 Hz, 1H), 3.00−2.75 (m, 4H), 2.19 (s, 6H), 1.20−1.05 (m, 12H). LC−MS m/z = 715 $[C_{41}H_{51}N_2O_7P + H]^+$. Anal. ($C_{41}H_{51}N_2O_7P \cdot 0.4H_2O$). C, H, N.

TR Binding Affinity Measurements. Recombinant TRα/RXRα and TRβ/RXRα heterodimers were generated by means of a baculovirus expression system (Invitrogen, Carlsbad, CA). cDNAs encoding TRα_1 (IMAGE, 2961613) and TRβ_1 (ATCC ID, 67244) were purchased from the American Type Culture Collection (Manassas, VA). cDNA for RXRα was purchased from Stratagene (San Diego, CA). The Bac-to-Bac baculovirus expression system was purchased from Invitrogen (Carlsbad, CA) and used to coexpress a His-tagged ligand binding domain of either TRα1 or TRβ1 with RXRα. A receptor binding assay using scintillation proximity assay (SPA) bead methodology was established using copper coated SPA beads (Amersham, Piscataway, NJ) and validated by characterizing the specificity and saturability of [^{125}I]T_3 binding. Displacement curves for compounds of interest were generated and analyzed using a four-parameter logistic curve fit model (SigmaPlot, Systat, CA).

Cholesterol Reducing Efficacy. Male Sprague−Dawley rats were purchased from Harlan (Indianapolis, IN). The rats were fed

a normal chow diet (Harlan 7001) supplemented with 1.5% cholesterol and 0.5% cholic acid (w/w) for at least 10 days prior to initiation of treatment. Plasma samples were obtained by tail nick. Efficacy was calculated as the percentage of difference from the total plasma cholesterol levels measured prior to dosing. Compounds were suspended in water, and 0.1 M NaOH was added dropwise until the compound was completely dissolved. All compounds were dosed using a volume of 1 mL/kg. Dose-response curves for compounds of interest were analyzed using a four-parameter logistic curve fit model (SigmaPlot, Systat, CA).

Analysis of Mitochondrial Glycerol-3-phosphate Dehydrogenase Activity. Mitochondria were isolated by differential centrifugation following homogenization (1:4, w/v) in cold 0.23 M sucrose, 70 mM mannitol, 50 mM HEPES, pH 7.4, as described.[59] mGPDH was measured using a spectrophotometric method with 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-phenyltetrazolium chloride as the terminal electron acceptor.[60] mGPDH activity was expressed as [(units of mGPDH)/min]/(μg of protein) with 1 unit defined as the amount of enzyme that converts 1.0 μmol of dihydroxyacetone phosphate to α-glycerophosphate per minute at pH 7.4 at 25 °C.

Rat Pharmacokinetics for Prodrug 72. Three groups (n = 5/group) of catheterized male Sprague−Dawley rats (250−300 g, 6−8 weeks old) were dosed with compound **72** intravenously (iv) at 3 mg/kg in 100% propylene glycol (PG) or orally (po) at 3 or 10 mg/kg in 100% polyethylene glycol (PEG)-400. Animals were fasted for 3 h prior to oral administration and were refed 1 h after dosing. Animals had free access to food prior to and during the iv evaluation. Blood samples were taken predose and at 5, 20, and 40 min and 1, 1.5, 2, 3, 5, 8, 12, and 24 h following iv administration of compound **72** or at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 24 h following oral administration. Plasma was prepared from blood samples by centrifugation and analyzed by liquid chromatography tandem mass spectrometry for prodrug **72** and phosphonic acid **22c** levels. The temporal profile of prodrug **72** and phosphonic acid **22c** concentrations in plasma was analyzed by noncompartmental methods. The oral bioavailability of prodrug **72** was calculated by comparison of the dose-normalized area under the curve (AUC) values of the plasma concentrations of compound **72** following oral administration with the AUC values of compound **72** following iv administration. The relative oral bioavailability of phosphonic acid **22c** was estimated by dividing the plasma AUC values of compound **22c** after oral dosing of prodrug **72** by the plasma AUC values of compound **22c** following iv administration of the prodrug **72**.

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Supporting Information Available: Elemental analysis results for compounds **13**, **16**, **22a**−**f**, **27**, **29**, **32**, **38a**−**c**, **40**, **45**, **48**, **57a**−**c**, **61a**,**b**, and **67**−**83** and mGPDH data. This material is available free of charge via the Internet at http://pubs.acs.org.

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