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Synthesis of Monofluorinated Analogues of Lysophosphatidic Acid

Yong Xu, Lian Qian, and Glenn D. Prestwich*

Department of Medicinal Chemistry and The Center for Cell Signaling, The University of Utah, 419 Wakara Way, Suite 205, Salt Lake City, Utah 84108-1257

gprestwich@pharm.utah.edu

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Lysophosphatidic acid (LPA, 1- or 2-acyl-*sn*-glycerol 3-phosphate) displays an intriguing cell biology that is mediated via interactions both with G-protein coupled seven transmembrane receptors and with the nuclear hormone receptor PPARγ. Synthesis and biological activities of fluorinated analogues of LPA are still relatively unknown. In an effort to identify receptor-selective LPA analogues and to document in detail the structure−activity relationships of fluorinated LPA isosteres, we describe a series of monofluorinated LPA analogues in which either the *sn*-1 or the *sn*-2 hydroxy group was replaced by fluorine, or the bridging oxygen in the monophosphate was replaced by an α-monofluoromethylene (−CHF−) moiety. The *sn*-1 or *sn*-2 monofluorinated LPA analogues were enantiospecifically prepared from chiral protected glycerol synthons, and the α-monofluoromethylene-substituted LPA analogues were prepared from a racemic epoxide with use of a hydrolytic kinetic resolution. The *sn*-2 and *sn*-1 fluoro LPA analogues were unable to undergo acyl migration, effectively "freezing" them in the *sn*-1-*O*-acyl or *sn*-2-*O*-acyl forms, respectively. The α-monofluoromethylene LPA analogues were unique new nonhydrolyzable ligands with surprising enantiospecific and receptor-specific biological readouts, with one compound showing a 1000-fold higher activity than native LPA for one receptor subtype.

Introduction

Lysophosphatidic acid (LPA, 1- or 2-acyl-*sn*-glycerol 3-phosphate) (Figure 1, **4**) is a naturally occurring phospholipid with a deceptively simple structure. It has received increasing attention due to the variety of biological responses that it evokes, including platelet aggregation, smooth-muscle contraction, changes in cell morphology, and mitogenesis.[1] LPA elicits these cellular events via signal transduction cascades downstream of its specific interactions with three G-protein-coupled receptors (GPCR) belonging to the *e*ndothelial *d*ifferentiation *g*ene (edg) family.[2] These receptors recently have been reclassified as LPA and sphingosine 1-phosphate receptors. In particular, edg-2, edg-4, and edg-7 are now the LPA-responsive receptors known as LPA_1, LPA_2, and LPA_3, respectively.[3,4] Surprisingly, LPA has a completely separate function as an intracellular lipid signal, based on its recent identification as a naturally occurring ligand for the nuclear hormone receptor PPARγ.[5]

LPA is released by activated platelets and accumulates in serum at low micromolar levels.[6] Substantial amounts of LPA also occur in the malignant ascites characteristic of ovarian cancer.[7,8] Signaling by LPA and other lysolipids is an important new direction for the development of new diagnostics and therapeutics to treat this disease.[9] Interestingly, the LPA found in serum and blood differs in that the ascites LPA appear to be enriched in 2-acyl LPA species.[7,10] Studying this 2-acyl LPA isoform has been difficult due to its chemical lability. Intramolecular acyl chain migration, which is facilitated by both acidic and basic conditions, affords an equilibrium mixture of

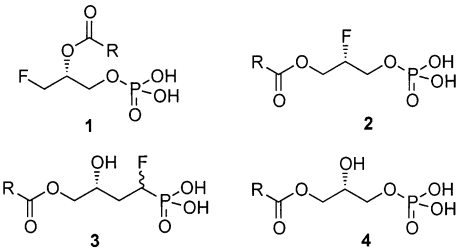

FIGURE 1. Metabolically stabilized monofluoro analogues (**1**−**3**) and parent *sn*-1-*O*-acyl lysophosphatidic acid (**4**).

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1-acyl- and 2-acyl-*sn*-glycerol-3-phosphates that favors the 1-acyl isoforms in approximately an 85:15 ratio at equilibrium.[11] Thus, the instability of 2-acyl-*sn*-glycerol-3-phosphate seriously compromises both isolation of naturally occurring species and determination of the activating ligand in structure−activity studies. Moreover, since the principal route of regulation of LPA involves its conversion to monoacylglycerol by lipid phosphate phosphatases (LPPs),[12−14] it has been difficult to evaluate what molecular LPA species are active and at what level in cells and tissues.

The isosteric substitution of essential hydroxyl groups by fluorine has been a mainstay of analogue design when metabolic stability is desired. It is particularly favored as a substituent when the presence of an electronegative atom is sufficient for the interaction of the ligand with the target protein.[15,16] Indeed, the high electron density gives rise to the ability of the fluorine substituent to act as an acceptor in intra- and intermolecular hydrogen bonds.[17−19] These interactions can result in modified binding to a receptor.[20] Therefore, we have developed a program to test the hypothesis that fluorinated analogues of LPA, particularly with fluorine in the *sn*-1 or *sn*-2 position, might mimic LPA as a biological ligand. Such mimics would not undergo intramolecular acyl chain migration, and could thus be useful in defining the regiochemical selectivity of LPA receptors for the acyl position.

Phosphate monoesters are susceptible to hydrolysis by the action of both general and specific phosphatases. In particular, since LPP is a major source of LPA catabolism,[12] we sought methods to create phosphatase-resistant LPA analogues. Phosphonates, in which the bridging oxygen is replaced by a carbon have been extensively investigated as phosphatase-stable phosphate mimics.[21] In one refinement of this strategy, [22,23] the bridging oxygen can be replaced by a CF_2 substituent. This is attractive as the fluorine atoms reintroduce the electronegativity that was lost due to the replacement of the oxygen atom. Although the α,α-difluorophosphonates have been more widely investigated in the last two decades, recent experimental and theoretical reports have indicated that an α-fluorophosphonate would be a better mimic for the phosphate.[24−26] The isoelectronic and isosteric replacement of oxygen by monofluoromethylene[27,28] in phosphate analogues confers metabolic stability and important features for receptor binding. Many monofluoromethylene-substituted phosphonate derivatives have been studied[25,29] as potential enzyme inhibitors and as probes for the elucidation of biochemical processes. Thus, we also describe herein a new approach to the synthesis of α-monofluoromethylene-substituted phospholipids, and we present the application of this approach to the preparation of a series of phosphatase-resistant LPA analogues.

Results and Discussion

The synthetic strategies of the target monofluoro compounds 1-fluorodeoxy-2-acyl-*sn*-glycerol-3-phosphate **1** and 1-acyl-2-fluorodeoxy-*sn*-glycerol-3-phosphate **2** were based on three design considerations. First, it was necessary to install the fluorine prior to acylation to avoid acyl chain migration during the synthesis. Second, we required both the natural 2*R* and unnatural 2*S* enantiomers of each LPA analogue to test for enantiospecific biological responses to 2-acyl or 2-fluoro stereoisomers. Third, for ease of synthetic manipulations, the deprotection of the penultimate dimethyl phosphate with trimethylsilane bromide (TMSBr) [30,31] was selected to permit incorporation of unsaturated acyl chains as well as to reveal the charged phosphate at the final step of the synthesis.

The key step for the synthesis of **1** and **2** was the stereoselective introduction of fluorine at the C-1 or C-2 position. Deoxyfluorination was accomplished by using diethylaminosulfur trifluoride (DAST),[32,33] an easily handled reagent that stereoselectively replaces hydroxyl with fluorine under mild conditions. Thus, 1-fluorodeoxy-(2*R*)-acyl-*sn*-glycerol-3-phosphates **1a** and **lb** were synthesized from commercially available (*R*)-isopropylideneglycerol **5**. Alcohol **5** was first phosphorylated with dimethylphosphoryl chloride in the presence of *t*-BuOK to give dimethyl phosphate **6** in 92% yield.[34,35] Next, phosphate **6** was converted to the 2-silyl ether 3-phosphate in three steps. Acetonide hydrolysis with *p*TsOH/MeOH gave a crude diol, which was converted directly to the bis-silyl ether **8** by treatment with *tert*-butyldimethylsilyl (TBS) chloride and imidazole in anhydrous DMF. The more labile primary TBS ether was then selectively cleaved with use of pyridium-HF in pyridine-

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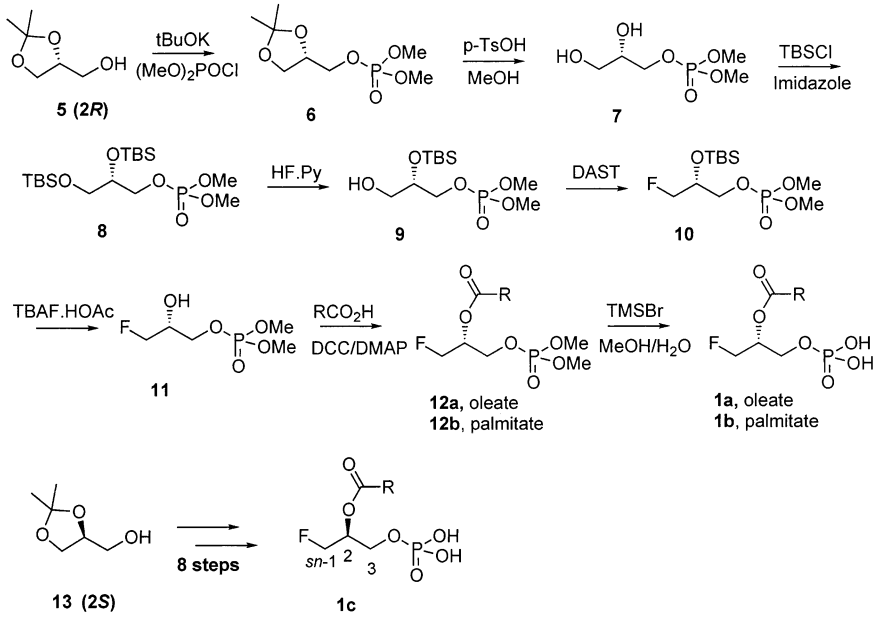
SCHEME 1. Synthesis of Enantiomeric *sn*-1-Fluoro-2-*O*-acyl LPA Analogues[a]



[a] The final LPA analogues in all schemes and figures are shown in the phosphoric acid form but are stored and used as mixed neutral sodium salts.

THF at room temperature.[36] By using an optimized selective deprotection, a 63% yield was obtained. Nucleophilic displacement of hydroxyl with DAST in anhydrous CH_2Cl_2 gave the corresponding monofluorinated compound **10**, without affecting the 2-TBS ether. The 2-hydroxyl was unmasked with use of *tetra*-(*n*-butyl)ammonium fluoride (TBAF) in THF; neutralization of TBAF with acetic acid permitted desilylation without phosphate migration.[37] DCC-promoted esterification of **11** with either oleic acid or palmitic acid provided good yields of esters **12a** and **12b**, which were purified to >99% homogeneity prior to deprotection. Finally, treatment of each ester **12** with TMSBr and subsequent addition of 5% aq methanol provided the desired fluorinated LPA analogues **1a** and **1b** in nearly quantitative yield. With use of the same procedure, the (2*S*)-LPA analogue **1c** was obtained from (*S*)-isopropylideneglycerol **13** in the analogous eight steps (5.6% overall yield).

We have found that the acid forms of these LPA analogues can be labile during storage or when made as stock solutions for biological evaluation. Thus, we have adopted a standard protocol to obtain a stable sodium salt form of each LPA analogue. For example, **1a** was dissolved in 1.0 M triethylammonium bicarbonate (TEAB) buffer (pH 8.0) to give a slightly cloudy solution, which was absorbed onto a sodium ion-exchange column (Dowex 50WX8-200 resin, neutral Na^+ form). The desired mixed neutral sodium salt of **1a** was eluted with Nanopure water. The product solution was lyophilized to give an amorphous white powder, which was stored in solid form at −80 °C. Aqueous or DMSO solutions of LPA analogues were prepared and used within several days to minimize hydrolysis or other decomposition.

The 1-acyl-(2*S*)-fluorodeoxy-*sn*-glycerol-3-phosphates **2a** and **2b** were synthesized from (*S*)-isopropylideneglycerol **13**. As described above for diol **7**, diol **14** was prepared by phosphorylation with dimethylphosphoryl chloride followed by acid hydrolysis. Initial unsuccessful attempts involved acylation of the 1-position followed by reaction with DAST at −78 °C to introduce the 2-fluoro group; extensive side reactions led us to abandon this short-cut. Instead, the primary alcohol was selectively protected as the *tert*-butyldiphenylsilyl (TBDPS) ether. Thus, treatment of diol **14** with the TBDPS chloride gave the *sn*-1 TBDPS ether **15**. Deoxyfluorination of **15** gave good yields of the 2-fluorinated product **16**. Deprotection of ether **16** with TBAF in THF gave alcohol **17**, which was esterified with either oleic or palmitic acids as described above to give the target protected LPA derivatives **18a** and **18b.** Deprotection of the phosphotriester with bromotrimethylsilane afforded the desired fluorinated LPA analogues **2a** and **2b**. Similarly, the enantiomeric (2*R*)-2-fluorodeoxy LPA analogues **2c** and **2d** were synthesized from (*R*)-isopropylideneglycerol **5**.

Current approaches to the synthesis of monofluoromethylene phosphonates include electrophilic fluorination (Selectorfluor, FN-$(SO_2Ph)_2$),[38,39] nucleophilic fluorination (DAST),[40,41] Arbuzov reactions with fluorohalomethanes,[42] transition metal catalyzed addition of diethyl monofluoroiodomethyl-phosphonate to alkene,[43,44]

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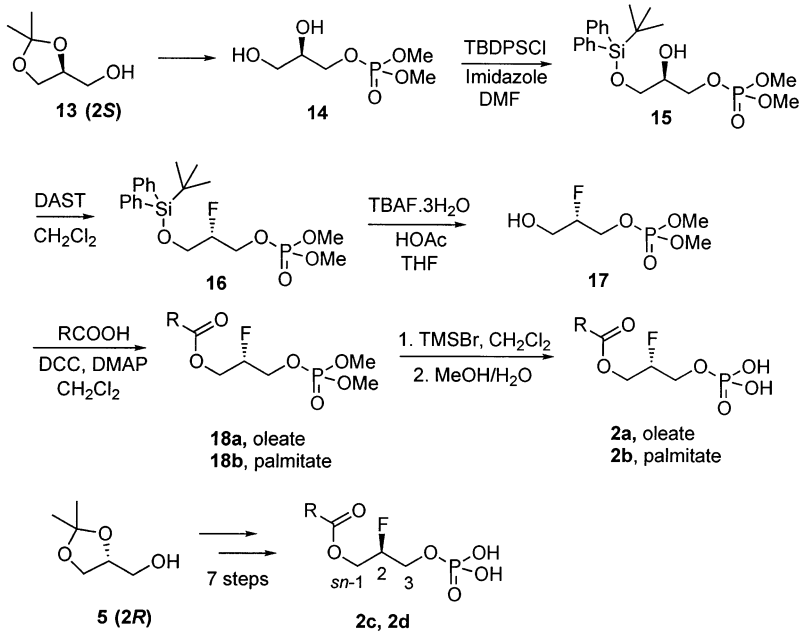
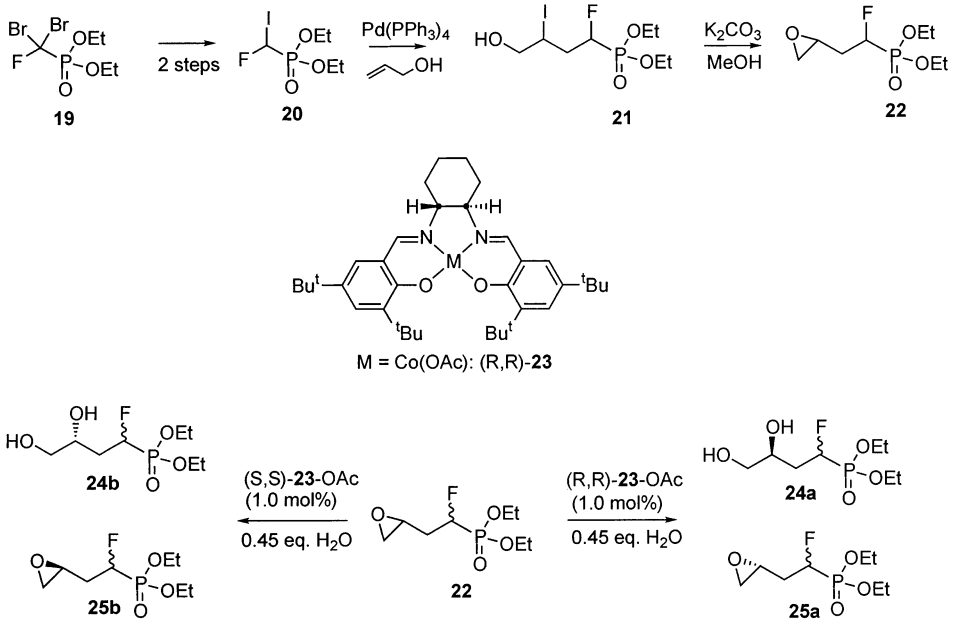
SCHEME 2. Synthesis of Enantiomeric *sn*-1-*O*-Acyl-2-fluoro LPA Analogues



SCHEME 3. Synthesis and Hydrolytic Kinetic Resolution of Fluorophosphonate Epoxide



and displacement of triflates or iodides by fluorosulfonyl-alkyl-phosphonates.[27] Recently, we have reported a facile and practical method for the synthesis of enantiomeric pure α,α-difluoromethylene phosphonate analogues of LPA by hydrolytic kinetic resolution (HKR) of a racemic epoxide.[45] We selected this strategy for the preparation of the α-monofluoromethylene phosphonate analogues **3**. Thus, as illustrated in Scheme 3, 1-fluoro-3,4-epoxybutylphosphonate **22** (IUPAC numbering) was prepared by addition of iodofluoromethylene-phosphonate **20** to allyl alcohol and subsequent base-induced cyclization of the iodohydrin **21** to epoxide **22**. The HKR reaction,[46−48] using two enantiomeric cobalt salen complexes **23** as catalysts, would be used for kinetic resolution of the terminal epoxide of **22** to obtain enantiomerically enriched diols **24a** and **24b**. These diols in turn would be mono-acylated to give the corresponding enantiomeric α-monofluoromethylene phosphonate LPA analogues **3**.

Scheme 3 shows the final synthetic route for these analogues. First, iodomonofluoromethyl phosphonate **20** was prepared in good yield from commercially available diethyl dibromofluoromethyl phosphonate **19** by tributylphosphine reduction and iodine quench of the intermediate zinc species.[44] Next, the tetrakis(triphenylphosphine)-palladium-catalyzed addition of phosphonate **20** to allyl

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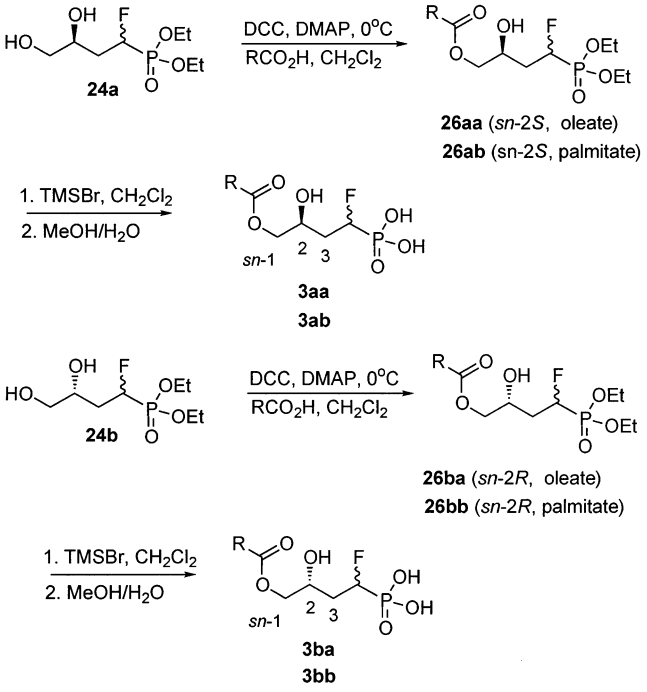
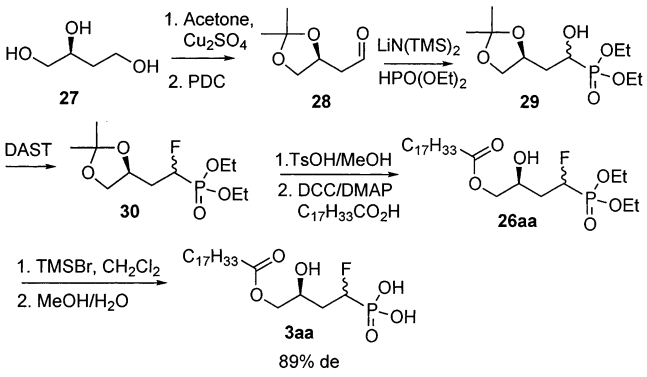
SCHEME 4. Conversion of Resolved Fluorophosphonate Diols to *sn*-1-*O*-Acyl α-Fluoromethylenephosphonate Analogues



alcohol in hexane gave the corresponding iodohydrin **21** in 79% yield. Treatment of the iodohydrin with dilute K_2CO_3/MeOH solution for 5 min at room temperature provided the desired epoxide **22** in good yield (72%).[49] It is important to note that the racemic epoxide is also a mixture of fluorine epimers at C-1, as demonstrated by the two equal multiplets in the ^{19}F NMR spectra of this and subsequent intermediates. Next, reaction of racemic epoxide **22** with 0.45 equiv of H_2O in a minimum volume of THF, in the presence of 1.0 mol % of (*R*,*R*)-**23**-OAc, gave diol **24a** in 90% ee and 73% isolated yield. Similarly, catalyst (*S*,*S*)-**23**-OAc provided the opposite configuration of diol **24b** in 89% ee and 90% yield. The epoxide and diol were readily separated by flash chromatography, providing a further extension of the scope of the HKR process, which was previously employed to prepare the difluoromethylene phosphonates.[45] Each diol was isolated as an inseparable, equimolar mixture of two diastereomers epimeric at C-1. For initial assessment of biological activity, the separation of this epimeric mixture at the C-1 phosphonate methylene was not required.

Regioselective acylation of the primary hydroxyl of diols **24** was readily accomplished (Scheme 4). Note that the numbering employed henceforth for the phosphonate LPA analogues **24**, **25**, **26**, and **3** employs the *sn*-glycerol nomenclature for clarity of comparison with other LPA derivatives. Thus, treatment of **24a** with 0.95 equiv of oleic acid and 1.2 equiv of DCC and DMAP in CH_2Cl_2 at 0 °C gave **26aa** in 42% yield, following chromatography to remove a small amount of diester. The corresponding palmitate **26ab** was similarly produced, as were the enantiomeric oleate **26ba** and palmitate **26bb**. Finally, LPA analogues **3** were obtained by dealkylation of the

SCHEME 5. Diastereoselective Synthesis of *sn*-1-*O*-Acyl α-Fluoromethylenephosphonate LPA Analogues



diethyl phosphonates **26** with excess TMSBr (10.0 equiv) for 8 h at room temperature.

Since we were unable to separate the diastereomeric 1-fluoro-3-hydroxyl isomers of compounds **24**, **26**, or **3**, we selected an alternative approach to prepare a diastereomerically enriched α-monofluorinated phosphonate. For this synthesis, (2*S*)-1,2,4-butanetriol **27** was protected as the isopropylidene acetal and oxidized with PDC to give aldehyde **28**.[50] The Pudovik reaction was then employed to introduce the C−P bond.[51] Thus, the anion of diethyl phosphite was added to aldehyde **28** at −20 °C to give two chromatographically inseparable α-hydroxyl phosphonates **29** in modest overall yield. This addition reaction occurred without diastereoselectivity, since two single sharp resonances at 25.37 and 24.47 ppm of equal intensity were observed in the ^{31}P NMR spectrum. This diastereomeric mixture was treated directly with DAST, which gave a pair of diastereomers in a 6.3:1 ratio as determined by both ^{31}P NMR and ^{19}F NMR in modest yield. Recently, Berkowitz also reported that DAST-mediated conversion of a nonbenzylic, secondary (α-hydroxyl)phosphonate to the (α-monofluoro)phosphonate proceeded with good diastereoselectivity.[40] After deprotection by acid hydrolysis and selective esterification, phosphonate **26aa** was obtained in >89% de. Finally, TMSBr deprotection gave the final product **3aa** showing >89% de. Since no reference materials were available, and NMR methods failed to define the relative geometries of the C−H bonds at C-1 and C-3, we cannot assign the absolute configuration at C-1 to this predominant stereoisomer at this time.

The preparation of receptor-specific agonists and antagonists for LPA receptors is an active area of ligand design. Structure−activity studies have demonstrated that analogues **31**and **32** (see Figure 2), lacking the 2-hydroxy group and structurally different analogues, such as the *N*-palmitoylserine and *N*-palmitoyltyrosine phosphoric acids **33** and **34**, are potent competitive antagonists of LPA receptor function in *Xenopus* oocytes.[52] However, as yet, a comprehensive analysis of fluorinated LPA analogues as selective agonists or antagonists for individual LPA receptors has not yet been reported. The monofluorinated analogues described herein,

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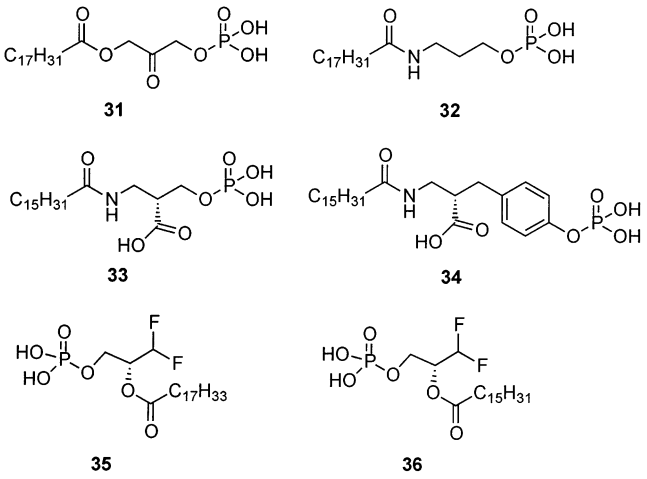

FIGURE 2. Known synthetic ligands with LPA-like activities.

TABLE 1. Activation of Platelet Aggregation for 1 μM *sn*-1-*O*-Oleoyl LPA (1, R = Oleoyl) and 1 μM of Each of Four LPA Analogues 2a−d[a]

compd	aggregation response
1 (R = oleoyl)	++
2a	+
2b	+
2c	−
2d	−
35	++
36	++

[a] Key: ++, strong aggregation response; +, weak but pronounced aggregation; −, no aggregation.

together with the 1,1-difluoro LPA derivatives[35] (Figure 2, **35** and **36**) and the α,α-difluoromethylene phosphonates[45] described previously, now provide a set of ligands to perform this comprehensive analysis.

Three biological activities have been evaluated for selected analogues: platelet activation, transmembrane LPA receptor activation, and nuclear PPARγ activation. Taken together, these assays demonstrate that different analogues may activate quite different LPA-mediated responses. First, platelet activation was evaluated by using a standard aggregometer assay,[53] in which activated platelets release additional LPA leading to platelet aggregation[1,6] (S. Smyth and A. Morris, personal communication). As shown in Table 1, *sn*-1-*O*-oleoyl LPA (**4**) and the two 1,1-difluoro analogues **35** and **36** (Figure 2)[35] were potent activators of platelet aggregation at 1 μM. In contrast, while the two (2*S*)-fluorodeoxy analogues **2a** and **2b** showed weak platelet activation, the enantiomeric (2*R*) analogues **2c** and **2d** were inactive.

Second, the LPA analogues were tested in insect cells expressing LPA_1, LPA_2, or LPA_3 receptors[54] (J. Aoki, K. Hama, Y. Xu, and G. D. Prestwich, in preparation). While compounds **1a**, **1b**, and **2a−d** failed to show either significant agonist or antagonist activity for any of the three isoforms, **1c** was found to be more potent than natural 18:1 LPA for the LPA_3 receptor[54] (J. Aoki, K. Hama, Y. Xu, and G. D. Prestwich, in preparation). Moreover, the α-monofluoromethylene-substituted LPA analogue **3aa** was 1000-fold more potent than natural 18:1 LPA for the LPA_3 receptor.[54] This response was enantiospecific, indicating that the α-fluorophosphonates are structurally informative and receptor-selective mimics for phosphate in LPA. The full biological data and enantioselectivity of the receptor recognition will be reported in due course (J. Aoki, K. Hama, Y. Xu, and G. D. Prestwich, in preparation).

Finally, the effects of monofluorinated *sn*-1 *O*-acyl LPA analogues **2a−d** were evaluated in a nuclear reporter assay in which monocytic cells were transfected with a luciferase construct activated by a PPARγ nuclear receptor response element.[5] As illustrated in Figure 3, analogues **2a−d** were essentially equipotent with *sn*-1-oleoyl-LPA **4** in this assay. Importantly, compounds inactive in the transmembrane receptor assays were fully active as nuclear receptor ligands. These data demonstrate that particular fluorine substitutions can give selective agonists for different LPA receptors, and that some, but not all, biological responses show both regioselectivity and enantioselectivity relative to the placement of the acyloxy and fluoro substituents.

In summary, we have described efficient methods for the preparation of monofluoro-substituted and α-monofluoromethylene phosphonate analogues of LPA from readily available precursors. The intriguing biological activity of LPA warrants a detailed evaluation of the fluorinated structure−activity relationships of LPA analogues for a variety of biological responses. Full descriptions of biological activity and the utility of analogues as migration-blocked or non-hydrolyzable LPA mimics will be reported in due course.

Experimental Section

General Procedures. Except where noted, all reagents were purchased commercially. Solvents were of reagent grade and were distilled before use: THF was dried by distillation from sodium-benzophenone ketyl and methylene chloride was distilled from CaH_2. Reactions were performed under an inert atmosphere (N_2 or Ar) unless otherwise indicated. NMR spectra were recorded at 400 (^{1}H), 101 (^{13}C), 162 (^{31}P), and 376 MHz (^{19}F), at 25 °C. Chemical shifts are reported relative to those of internal chloroform (δ_H 7.24), methanol (δ_H 4.78), or tetramethylsilane (δ_H 0.00) for ^{1}H; chloroform (δ_C 77.0) or methanol (δ_C 49.0) for ^{13}C; and $CFCl_3$ for ^{19}F (δ_F 0.00); 85% H_3PO_4 (δ_P 0.00) was used as an external standard. Optical rotations were obtained at ambient temperature.

Dimethyl 1,2-(*S*)-Isopropylidene-*sn*-glycerol-3-phosphate (6). *t*-BuOK (1.274 g, 11.35 mmol) was added to a stirred solution of (*R*)-isopropylideneglycerol (1.00 g, 7.57 mmol) and dimethyl chlorophosphate (1.367 g, 9.46 mmol) in CH_2Cl_2 (25 mL), and the solution was stirred at room temperature for 1 h (complete by TLC). A saturated aq solution of NH_4Cl (40 mL) was added, the solution was stirred for 10 min, and the aq phase was extracted three times with CH_2Cl_2 (30 mL); the organic solution was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified on silica gel by elution with diethyl ether to give 1.62 g (6.75 mmol, 92% yield, R_f 0.30, diethyl ether) of pure product as a colorless oil. $\delta_H(CDCl_3)$: 4.22 (m, 1H), 3.95 (m, 4H), 3.69 (s, 3H), 3.66 (s, 3H), 1.33 (s, 3H), 1.24 (s, 3H). $\delta_H(CDCl_3)$: 106.69 (s), 73.88 (d, J = 7.6 Hz), 67.36 (d, J = 5.3 Hz), 65.84 (s), 54.23 (d, J = 3.8 Hz), 26.51 (s), 25.06 (s). $\delta_P(CDCl_3)$: 2.23 (s). $[\alpha]^{20}_D$ +2.28° (*c* 2.08, MeOH).

(53) Coller, B.; Peerschke, E.; Scudder, L.; Sullivan, C. *J. Clin. Invest.* **1983**, *72*, 325−338.
(54) Prestwich, G. D.; Xu, Y.; Qian, L.; Hama, K.; Aoki, J. Annual Meeting, ASBMB, San Diego, CA, 2003; poster 628.20.

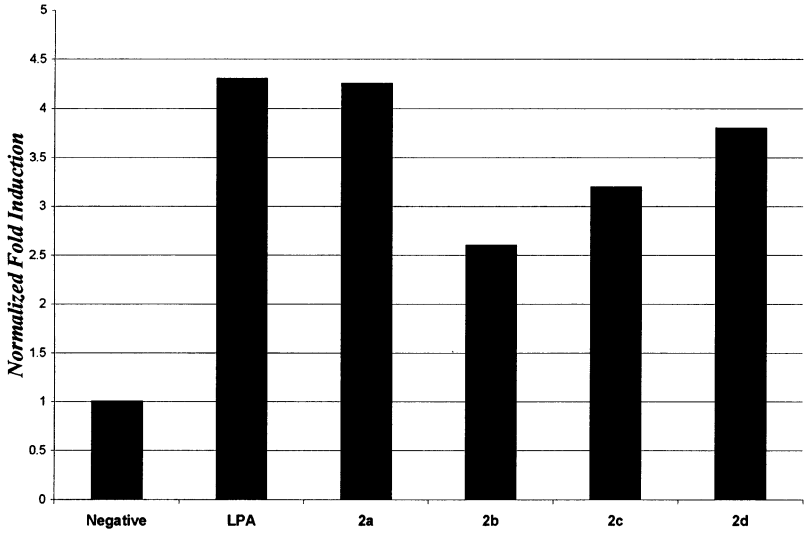

FIGURE 3. The PPARγ response element luciferase reporter stimulation in a cell-based assay (see Experimental Section) is shown at 5 μM *sn*-1-*O*-oleoyl LPA (**4**, R = oleoyl) and 5 μM of each of four LPA analogues **2a**−**d**.

Dimethyl (2*S*)-1,2-Di(tetrabutyldimethylsilyl)-*sn*-glycerol-3-phosphate (8). TsOH (54 mg, 0.28 mmol, 0.10 eq) was added to a solution of **6** (0.678 g, 2.83 mmol) in MeOH (10 mL), and the solution was stirred at room temperature for 24 h. After addition of NEt_3 (0.1 mL), the solvent was removed under reduced pressure. Following addition of anhydrous DMF (3 mL), imidazole (0.577 g, 8.48 mmol, 3.0 equiv), and *tert*-butyldimethylsilyl chloride (TBSCl) (1.107 g, 7.35 mmol, 2.8 equiv), the reaction mixture was stirred at room temperature for an additional 36 h. The solution was diluted with water (15 mL) and ethyl acetate (20 mL), and the aqueous layer was separated and extracted three times with ethyl acetate (30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo, and the residue was purified on silica gel (*n*-hexane/ethyl acetate 4:1, R_f 0.13) to afford 0.804 g (1.88 mmol, 67%) of a colorless liquid. $\delta_H(CdCl_3)$: 4.08 (m, 1H), 3.89 (m, 1H), 3.80 (m, 1H), 3.73 (d, J = 1.2 Hz, 3H), 3.70 (d, J = 1.2 Hz, 3H), 3.51 (d, J = 5.2 Hz, 3H), 0.84 (s, 9H), 0.84 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H). $\delta_C(CdCl_3)$: 84.77 (d, J = 6.1 Hz), 77.50 (d, J = 7.6 Hz), 74.36 (d, J = 6.2 Hz), 69.50 (s), 67.52 (d, J = 4.5 Hz), 59.69 (d, J = 6.3 Hz), 31.34 (s), 31.20 (s), 31.22 (s), 23.75 (s), 23.57 (s), 0.77 (s), 0.68 (s), 0.02 (s), 0.00 (s). $\delta_P(CdCl_3)$: 2.42 (s). MS (CI) *m*/*z* 429.1 (M^+ + 1, 100.00). HRMS for $C_{17}H_{42}PSi_2O_6$: found 429.2244, calcd 429.2230. $[\alpha]^{20}_D$ +0.18° (*c* 2.25, MeOH).

Dimethyl (2*S*)-(Tetrabutyldimethylsilyl)-*sn*-glycerol-3-phosphate (9). The HF·pyridine complex (70%, 0.31 mL) was added to a mixture of pyridine (1.40 mL) and a solution of the bis-TBS ether **8** (0.759 g, 1.77 mmol) in THF (10 mL). The reaction mixture was stirred for 24 h. After completion of the reaction (TLC), the solution was diluted with ethyl acetate (50 mL), washed with saturated NaCl solution (5 mL), and dried over anhydrous Na_2SO_4. After removal of the solvents, the residue was purified on silica gel (ethyl acetate, R_f 0.23) to afford a colorless liquid: 0.254 g (0.814 mmol, 46%). $\delta_H(CdCl_3)$: 3.93 (m, 2H), 3.82 (m, 1H), 3.69 (d, J = 1.2 Hz), 3.66 (d, J = 1.2 Hz, 3H), 3.52 (dd, J = 8.4, 4.4 Hz, 2H), 0.79 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H). $\delta_C(CdCl_3)$: 76.06 (d, J = 7.6 Hz), 72.40 (d, J = 6.1 Hz), 67.93 (s), 59.29 (d, J = 6.1 Hz), 30.57 (s), 22.91 (s), 0.11 (s), 0.00 (s). $\delta_P(CdCl_3)$: 2.788 (s). MS (CI) *m*/*z* 315.1 (M^+ + 1, 100.00). HRMS for $C_{11}H_{28}SiPO_6$: found 315.1412, calcd 315.1414. $[\alpha]^{20}_D$ +0.28° (*c* =1.08, MeOH).

1-Phospho-2(*S*)-(tetrabutyldimethylsilyl)-3-fluorine-propane-1,2-diol Dimethyl Ester (10). To a mixture of 0.035 g (0.220 mmol) of DAST and 2 mL of dry CH_2Cl_2 at −78 °C was added dropwise a solution of alcohol (0.049 g, 0.157 mmol) in 1 mL of dry CH_2Cl_2. The mixture was stirred at −78 °C for 1 h, then at room temperature for an additional 1 h. To the mixture was added 0.2 mL of methanol followed by neutralization with solid $NaHCO_3$. After concentration in vacuo, the residue was purified on silica gel (hexanes−ethyl acetate 1:1, R_f 0.25) to afford 0.026 g. (0.083 mmol, 53%) as a colorless oil. $\delta_H(CdCl_3)$: 4.35 (ddd, 1H), 4.24 (ddd, 1H), 4.02−3.86 (m, 3H), 3.69 (d, J = 1.2 Hz, 3H), 3.66 (d, J = 1.2 Hz, 3H), 0.79 (s, 9H), 0.05 (s, 6H). $\delta_C(CdCl_3)$: 88.46 (d, J = 172.6 Hz), 74.76 (dd, J = 20.7, 8.5 Hz), 72.26 (t, J = 6.5 Hz), 59.31 (d, J = 7.6 Hz), 30.55 (s), 22.98 (s), 0.00 (s). $\delta_P(CdCl_3)$: 2.252 (s). $\delta_F(CdCl_3)$: 230.50 (td, J = 47.0, 20.7 Hz). MS (CI) *m*/*z* 317.1 (M^+ + 1, 100.00). HRMS for $C_{11}H_{27}FSiPO_5$: found 317.1344, calcd 317.1349. $[\alpha]^{20}_D$ +0.23° (*c* 0.33, MeOH).

1-Phospho-2(*S*)-(oleoyl)-3-fluorine-propane-1,2-diol Dimethyl Ester (12a). A solution of **10** (18 mg, 0.058 mmol) in THF (2 mL) was treated consecutively with acetic acid (13 μL, 0.231 mmol) and tetrabutylammoniumfluoride trihydrate (73 mg, 0.231 mmol) at room temperature. After the solution was stirred for 18 h the reaction was complete (TLC control), the solvent was then evaporated under reduced pressure and the crude product was purified on a short column of silica gel to afford a colorless liquid. To the crude alcohol **11** and 42 mg (47 μL, 0.147 mmol) of oleic acid in dry CH_2Cl_2 (1 mL) at room temperature was added dropwise a solution of DCC (30 mg, 0.147 mmol) and DMAP (6.0 mg, 0.048 mmol) in dry CH_2Cl_2 (1 mL). The solution was stirred at room temperature for 18 h, filtered, concentrated in vacuo, and the residue was purified on silica gel (*n*-hexanes−ethyl acetate 1:1, R_f 0.28) to afford 12 mg of a waxy solid (0.026 mmol, 45%). $\delta_H(CdCl_3)$: 5.28 (m, 2H), 5.14 (dm, J = 20.8 Hz, 1H), 4.51 (dd, J = 46.8, 4.0 Hz, 2H), 4.15 (m, 2H), 3.73 (d, J = 2.4 Hz, 3H), 3.70 (d, J = 2.4 Hz, 3H), 2.30 (t, J = 7.2 Hz, 2H), 1.90 (m, 4H), 1.56 (m, 4H), 1.14 (m, 20H), 0.81 (t, J = 6.4 Hz, 3H). $\delta_C(CdCl_3)$: 173.00 (s), 130.26 (s), 129. 93 (s), 80.22 (d, J = 172.0 Hz), 70.29 (d, J = 28.6 Hz), 64.64 (t, J = 6.5 Hz), 54.74 (s), 54.68 (s), 34.32 (s), 34.17 (s), 32.12 (s), 29.98 (s), 29.90 (s), 29.53 (s), 29.36 (s), 29.30 (s), 29.24 (s), 27.44 (s), 27.38 (s), 25.84 (s), 25.16 (s), 25.01 (s), 22.89 (s), 14.32 (s). $\delta_P(CdCl_3)$: 2.185 (s). $\delta_F(CdCl_3)$: −234.50 (td, J = 47.0, 20.7 Hz). MS (CI) *m*/*z* 467.0 (M^+ + 1, 100.00), 341.2 (M^+ − $OPO(OMe)_2$, 56.20). HRMS for $C_{23}H_{45}FPO_6$: found 467.2921, calcd 467.2904. $[\alpha]^{20}_D$ +0.69° (*c* 0.36, MeOH).

1-Phospho-2(*S*)-(palmitoyl)-3-fluorine-propane-1,2-diol Dimethyl Ester (12b). A solution of **10** (22 mg, 0.071 mmol) in THF (2 mL) was treated consecutively with acetic acid (16 μL, 0.28 mmol) and tetrabutylammoniumfluoride trihydrate (89 mg, 0.28 mmol) at room temperature. The crude alcohol **11** was directly esterified with palmitic acid (following the protocol above for **12a**) and purified on silica gel (*n*-hexanes−ethyl acetate 1:1, R_f 0.28) to afford 11 mg of a waxy

solid (0.025 mmol, 35%). $\delta_H(CdCl_3)$: 5.20 (dm, J = 21.0 Hz, 1H), 4.57 (dd, J = 46.8, 4.0 Hz, 2H), 4.25 (m, 2H), 3.79 (d, J = 2.8 Hz, 3H), 3.76 (d, J = 2.4 Hz, 3H), 2.36 (t, J = 9.6 Hz, 2H), 1.93 (m, 2H), 1.62 (m, 4H), 1.24 (m, 20H), 0.87 (t, J = 9.6 Hz, 3H). $\delta_C(CdCl_3)$: 173.0 (s), 80.84 (d, J = 173.4 Hz), 70.27 (d, J = 7.64 Hz), 70.07 (d, J = 7.4 Hz), 64.64 (t, J = 6.7 Hz), 54.74 (s), 54.68 (s), 29.88−29.86 (m), 29.81 (s), 29.57 (s), 29.45 (s), 29.27 (s). $\delta_P(CdCl_3)$: 2.171 (s). $\delta_F(CdCl_3)$: −234.49 (td, J = 47.0, 21.0 Hz). MS (CI) m/z 441.3 ($M^+ + 1$, 20.84), 225 ($M^+ - H_2O - C_{12}H_{25}$, 100.00). HRMS for $C_{21}H_{43}FPO_6$: found 441.2790, calcd 441.2781. $[\alpha]^{20}_D$ +0.91° (*c* 0.29, MeOH).

1-Phospho-2(*S*)-(oleoyl)-3-fluorine-propane-1,2-diol (1a). A thoroughly dried sample of ester **12a** (8 mg, 0.017 mmol, 5 h under high vacuum) was dissolved in dry methylene chloride (1 mL) at room temperature. Next, bromotrimethylsilane (TMSBr, 9 μL, 0.052 mmol) was added via syringe and the reaction was stirred for 4 h. When TLC indicated that all of the reactant had been consumed, the solvent was removed under reduced pressure and the residue was dried in vacuo. The residue was dissolved in 95% methanol (1 mL) for 1 h, the solvent was then removed under reduced pressure, and the product was dried in vacuo to give 6 mg of a colorless oil (CH_2Cl_2:CH_3OH:H_2O 20:10:1, R_f 0.39, 0.014 mmol, 82% yield). Without further purification, the purity of this product **1a** was >98% homogeneous as determined by TLC and NMR (^1H, ^{13}C, ^{19}F, and ^{31}P). $\delta_H(Cd_3OD)$: 5.24 (m, 2H), 5.11 (dm, J = 20.4 Hz, 1H), 4.49 (dd, J = 47.2, 4.8 Hz, 2H), 4.03 (m, 2H), 2.29 (t, J = 7.6 Hz, 2H), 1.93 (m, 4H), 1.61−1.54 (m, 4H), 1.20 (m, 17H), 0.81 (t, J = 6.4 Hz, 3H). $\delta_C(Cd_3OD)$: 173.80 (s), 130.86 (s), 130.53 (s), 80.72 (d, J = 171.9 Hz), 70.79 (d, J = 28.4 Hz), 65.09 (t, J = 6.5 Hz), 34.75 (s), 34.60 (s), 33.72 (s), 33.55 (s), 31.87 (s), 29.65 (s), 29.60 (s), 29.41 (s), 29.25 (s), 29.15 (s), 29.08 (s), 28.98 (s), 28.91 (s), 26.93 (s), 14.35 (s). $\delta_P(Cd_3OD)$: 0.843 (s). $\delta_F(Cd_3OD)$: −235.96 (td, J = 47.0, 20.7 Hz). m/z 438.0 (M^+, 0.30), 314.2, ($M^+ - OPO(OH)_2$, 100.00), 157, ($M^+ - OCOR$, 62.91). MS (CI) m/z 439.3 ($M^+ + 1$, 45.34). HRMS for $C_{21}H_{41}FO_6P$ ($M^+ + 1$): found 439.2634, calcd 439.2625. $[\alpha]^{20}_D$ +0.57° (*c* 0.12, MeOH).

The labile acid forms of these analogues were then converted to mixed neutral sodium salts. Thus, product **1a** was dissolved in 2 mL of 1.0 M triethylammonium bicarbonate (TEAB) buffer (pH 8.0) to give a slightly cloudy solution, which was absorbed to a sodium ion-exchange column (Dowex 50WX8-200 resin, neutral Na^+ form). The desired mixed neutral sodium salt of **1a** was eluted with Nanopure water. The product solution was lyophilized to give sodium salt as white amorphous solid, which was stored in solid form at −80 °C. Aqueous solutions of LPA analogues were prepared and used within several days to minimize hydrolysis and acyl migration (when possible). All LPA analogues described herein were converted to the corresponding sodium salts in the same procedure.

1-Phospho-2(*S*)-(palmitoyl)-3-fluorine-propane-1,2-diol (1b). Deprotection of **12b** (11 mg, 0.025 mmol, 5 h drying at 0.01 mg Hg) was conducted as described above for **12a** to give 6 mg of phosphate **1b** as a colorless oil (CH_2Cl_2:CH_3OH:H_2O 20:10:1, R_f 0.37, 0.019 mmol, 78% yield). $\delta_H(Cd_3OD)$: 5.22 (dm, J = 21.0 Hz, 1H), 4.58 (dd, J = 47.2, 3.2 Hz, 2H), 4.25 (m, 2H), 2.36 (t, J = 9.6 Hz, 2H), 1.93 (m, 2H), 1.76 (m, 2H), 1.62 (m, 4H), 1.29 (m, 18H), 0.87 (t, J = 6.8 Hz, 3H). $\delta_C(Cd_3OD)$: 173.40 (s), 81.24 (d, J = 173.3 Hz), 70.67 (d, J = 7.5 Hz), 70.47 (d, J = 7.4 Hz), 64.95 (t, J = 6.6 Hz), 32.78 (s), 32.14 (s), 29.93 (s), 29.88 (s), 29.71 (s), 29.59 (s), 25.26 (s), 25.00 (s), 24.63 (s), 22.91 (s), 14.32 (s). $\delta_P(Cd_3OD)$: 1.742 (s). $\delta_F(Cd_3OD)$: −234.63 (td, J = 46.0, 21.0 Hz). MS (CI) m/z 413.3 ($M^+ + 1$, 51.22). HRMS for $C_{19}H_{39}FO_6P$ ($M^+ + 1$): found 413.2479, calcd 413.2468 $[\alpha]^{20}_D$ +0.81° (*c* 0.14, MeOH). The compound was converted to the sodium salt by ion exchange and stored in solid form at −80 °C as described for **1a**.

1-Phospho-2(*S*)-(oleoyl)-3-fluorine-propane-1,2-diol (1c). Colorless oil, $\delta_H(Cd_3OD)$: 5.24 (m, 2H), 5.11 (dm, J = 20.4 Hz, 1H), 4.49 (dd, J = 47.2, 4.8 Hz, 2H), 4.03 (m, 2H), 2.29 (t, J = 7.6 Hz, 2H), 1.93 (m, 4H), 1.61−1.54 (m, 4H), 1.20 (m, 17H), 0.81 (t, J = 6.4 Hz, 3H). $\delta_C(Cd_3OD)$: 173.80 (s), 130.86 (s), 130.53 (s), 80.72 (d, J = 171.9 Hz), 70.79 (d, J = 28.4 Hz), 65.09 (t, J = 6.5 Hz), 34.75 (s), 34.60 (s), 33.72 (s), 33.55 (s), 31.87 (s), 29.65 (s), 29.60 (s), 29.41 (s), 29.25 (s), 29.15 (s), 29.08 (s), 28.98 (s), 28.91 (s), 26.93 (s), 14.35 (s). $\delta_P(Cd_3OD)$: 0.840 (s). $\delta_F(Cd_3OD)$: −235.96 (td, J = 46.6, 20.6 Hz). $[\alpha]^{20}_D$ −0.71° (*c* 0.29, MeOH). The compound was converted to the sodium salt by ion exchange and stored in solid form at −80 °C as described for **1a**.

Dimethyl 1-(Tetrabutyldiphenylsilyl)-2-(*R*)-*sn*-glycerol-3-phosphate (15). TsOH (0.594 g, 3.0 mmol, 0.15 equiv) was added to a solution of dimethyl 1,2-(*R*)-isopropylidene-*sn*-glycerol-3-phosphate (4.80 g, 20.00 mmol) in MeOH (100 mL), and the solution was stirred at room temperature for 24 h. Following addition of solid $NaHCO_3$, the mixture was filtered, concentrated in vacuo, and purified on silica gel (methanol: ethyl acetate 1:5, R_f 0.26) to afford 3.64 g (18.2 mmol, 91%) of diol **14** as a colorless liquid. To a solution of the crude diol **14** (3.45 g, 17.25 mmol) in anhydrous DMF (120 mL) was added imidazole (3.41 g, 50.0 mmol, 2.9 equiv) and TBDPS chloride (6.16 g, 22.4 mmol, 1.3 equiv). The reaction mixture was stirred at 0 °C for 8 h, then at room temperature for 12 h. The solution was diluted with ethyl acetate (100 mL), and the solution was washed with saturated aq NH_4Cl solution and brine. After drying with anhydrous Na_2SO_4, the organic layer was concentrated in vacuo and purified on silica gel (ethyl acetate, R_f 0.48) to afford 5.10 g of a colorless liquid (11.68 mmol, 68%). $\delta_H(CDCl_3)$: 7.65 (m, 4H), 7.36 (m, 6H), 4.16 (m, 2H), 3.93 (m, 1H), 3.71 (d, J = 3.0 Hz, 3H), 3.68 (d, J = 2.0 Hz, 3H), 1.04 (s, 9H). $\delta_C(CDCl_3)$: 135.20 (s), 135.18 (s), 132.74 (s), 132.73 (s), 129.51 (s), 127.47 (s), 70.20 (d, J = 6.1 Hz), 68.52 (d, J = 6.1 Hz), 63.61 (s), 54.05 (dd, J = 6.1, 2.3 Hz), 26.49 (s), 18.88 (s). $\delta_P(CDCl_3)$: 2.869 (s). MS (CI) m/z 438.9 ($M^+ + 1$, 20.62), 380.9 ($M^+ - C_4H_9$, 39.84), 360.9 ($M^+ - C_6H_5$, 100.00). HRMS for $C_{21}H_{32}O_6PSi$ ($M^+ + 1$): found 439.1685, calcd 439.1706. $[\alpha]^{20}_D$ −0.77 (c 0.31, MeOH).

1-Phospho-2(*S*)-fluorine-3-(tetrabutyldiphenylsilyl)-propane-1,3-diol Dimethyl Ester (16). To a mixture of DAST (1.77 g, 10.96 mmol) and 50 mL of dry CH_2Cl_2 at −78 °C was added dropwise a solution of alcohol (4.00 g, 9.13 mmol) in 20 mL of dry CH_2Cl_2. The mixture was stirred at −78 °C for 1 h, followed by 1 h at room temperature. The mixture was poured into a stirred mixture of saturated $NaHCO_3$ and ice chips, then extracted with CH_2Cl_2. The extract was washed with H_2O, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The oil was purified on silica gel (hexanes: ethyl acetate 1:1, R_f 0.19) to afford 1.53 g (3.47 mmol, 38%) of **16** as a colorless liquid. $\delta_H(CDCl_3)$: 7.64 (m, 4H), 7.42 (m, 6H), 4.71 (dm, J = 47.6 Hz, 1H), 4.30 (dm, J = 23.6 Hz, 2H), 3.83 (m, 2H), 3.76 (d, J = 2.4 Hz, 3H), 3.68 (d, J = 2.4 Hz, 3H), 1.04 (s, 9H). $\delta_C(CDCl_3)$: 135.55 (s), 135.49 (s), 132.79 (s), 132.67 (s), 129.90 (s), 127.81 (s), 127.79 (s), 91.17 (dd, J = 177.2, 6.9 Hz), 66.33 (dd, J = 23.7, 5.3 Hz), 62.27 (d, J = 25.3 Hz), 54.40 (d, J = 6.1 Hz), 26.68 (s), 19.19 (s). $\delta_F(CDCl_3)$: −196.16 (1F, m). $\delta_P(CDCl_3)$: 2.278 (s). MS (CI) m/z 383.0 ($M^+ - C_4H_9$, 29.86), 363.0 ($M^+ - C_6H_5$, 100.00). HRMS for $C_{17}H_{21}FO_5PSi$ ($M^+ - C_4H_9$): found 383.0875, calcd 383.0880. $[\alpha]^{20}_D$ −4.88° (*c* 0.42, MeOH).

1-Phospho-2(*S*)-fluorine-propane-1,3-diol Dimethyl Ester (17). A solution of **16** (860 mg, 1.972 mmol) in THF (50 mL) was treated consecutively with acetic acid (0.46 mL, 7.888 mmol) and tetrabutylammoniumfluoride trihydrate (2.489 g, 7.888 mmol) at room temperature. After the solution was stirred for 16 h the reaction was complete (TLC), and the mixture was concentrated and passed through a silica column (ethyl acetate, R_f 0.20) to afford 0.342 g (1.69 mmol, 86%) of **17** as a colorless liquid. $\delta_H(CDCl_3)$: 4.67 (dm, J = 48.0 Hz, 1H), 4.23 (ddd, J = 22.4, 7.6, 4.4 Hz, 2H), 3.77 (dm, J = 19.6 Hz, 2H), 3.75 (d, J = 2.0 Hz, 3H), 3.72 (d, J = 2.0 Hz, 3H), 3.48 (br, 1H). $\delta_C(CDCl_3)$: 91.32 (dd, J = 174.8, 6.1 Hz), 66.02 (dd, J = 23.7, 5.3 Hz), 60.53 (d, J = 23.8 Hz), 54.54 (dd, J = 6.1, 3.8 Hz). $\delta_F(CDCl_3)$: −197.66 (1F, m). $\delta_P(CDCl_3)$: 2.453 (s).

MS (CI) *m/z* 203.1 ($M^+ + 1$, 100.00). HRMS for $C_5H_{12}FO_5P$ ($M^+ + 1$): found 203.0476, calcd 203.0485.

1-Phospho-2(*S*)-fluorine-3-(oleoyl)-propane-1,3-diol Dimethyl Ester (18a). To a solution of crude alcohol **17** (73 mg, 0.361 mmol) with oleic acid (113 mg, 0.397 mmol) in dry CH_2Cl_2 (3 mL) at room temperature was added dropwise a solution of DCC (112 mg, 0.542 mmol) and DMAP (27 mg, 0.217 mmol) in dry CH_2Cl_2 (3 mL). The solution was stirred at room temperature for 16 h and filtered, the solvent was removed, and the residue was purified on silica gel (*n*-hexanes: ethyl acetate 1:2, R_f 0.30) to afford 162 mg (0.347 mmol, 96%) of **18a** as a waxy solid. $\delta_H(CDCl_3)$: 5.28 (m, 2H), 4.80 (dm, J = 47.6 Hz, 1H), 4.24 (m, 4H), 3.74 (s, 3H), 3.72 (s, 3H), 2.86 (t, J = 7.2 Hz), 1.94 (m, 4H), 1.56 (m, 2H), 1.22 (m, 20H), 0.81 (t, J = 8.0 Hz, 3H). $\delta_C(CDCl_3)$: 173.07 (s), 129.87 (s), 129.57 (s), 88.67 (dd, J = 178.0, 7.6 Hz), 65.77 (dd, J = 24.5, 5.3 Hz), 61.97 (d, J = 23.7 Hz), 54.39 (d, J = 6.1 Hz), 33.80 (s), 31.77 (s), 29.63 (s), 29.54 (s), 29.38 (s), 29.18 (s), 29.00 (s), 28.94 (s), 28.92 (s), 27.07 (s), 27.02 (s), 24.67 (s), 22.54 (s), 13.96 (s). $\delta_F(CDCl_3)$: −195.98 (1F, m). $\delta_P(CDCl_3)$: 2.151 (s). MS (CI) *m/z* 467.4 ($M^+ + 1$, 100.00), 341.3 ($M^+ - C_2H_6PO_4$, 32.11). HRMS for $C_{23}H_{45}FO_6P$ ($M^+ + 1$): found 467.2891, calcd 467.2938. $[\alpha]^{20}_D$ −1.92° (*c* 2.52, MeOH).

1-Phospho-2(*S*)-fluorine-3-(palmitoyl)-propane-1,3-diol Dimethyl Ester (18b). The same procedure was followed as for **18a** to give **18b** as a waxy solid (*n*-hexanes:ethyl acetate 1:2, R_f 0.30; 139 mg, 0.316 mmol, 91%). $\delta_H(CD_3Cl)$: 4.77 (dm, J = 48.0 Hz, 1H), 4.17 (m, 4H), 3.77 (s, 3H), 3.68 (s, 3H), 2.26 (t, J = 7.6 Hz, 2H), 1.53 (m, 2H), 1.16 (m, 24H), 0.78 (t, J = 6.4 Hz, 3H). $\delta_C(CD_3OD)$: 173.43 (s), 88.57 (dd, J = 178.7, 7.6 Hz), 65.87 (dd, J = 23.8, 5.4 Hz), 61.92 (d, J = 23.8 Hz), 54.43 (d, J = 6.1 Hz), 33.77 (s), 31.72 (s), 29.49 (s), 29.45 (s), 29.39 (s), 29.25 (s), 29.16 (s), 29.03 (s), 28.89 (s), 24.62 (s), 22.48 (s), 13.87 (s). $\delta_F(CD_3OD)$: −196.11 (1F, m). $\delta_P(CD_3OD)$: 1.977 (s). MS (CI) *m/z* 441.3 ($M^+ + 1$, 100.00), 315.3 ($M^+ - C_2H_6PO_4$, 38.53). HRMS for $C_{21}H_{43}FO_6P$ ($M^+ + 1$): found 441.2770, calcd 441.2781. $[\alpha]^{20}_D$ −1.25° (*c* 1.25, $CHCl_3$).

1-Phospho-2(*S*)-fluorine-3-oleoyl-propane-1,3-diol (2a). Following the same procedure used above for **1a** afforded analogue **2a** as a white solid in 86% yield. $\delta_H(CD_3OD/CDCl_3$, 2/1): 5.32 (m, 2H), 4.82 (dm, J = 48.0 Hz, 1H), 4.37 (m, 2H), 4.05 (ddd, J = 48.0, 5.8, 5.2 Hz, 2H), 2.35 (t, J = 7.6 Hz, 3H), 2.00 (m, 4H), 1.62 (m, 2H), 1.29 (m, 20H), 0.87 (t, J = 6.4 Hz, 3H). $\delta_C(CD_3OD/CDCl_3$, 2/1): 174.10 (s), 129.86 (s), 129.69 (s), 90.70 (dd, J = 175.0, 7.6 Hz), 64.47 (dd, J = 24.5, 5.4 Hz), 64.13 (d, J = 22.2 Hz), 34.63 (s), 32.64 (s), 30.45 (s), 30.40 (s), 30.22 (s), 30.03 (s), 29.97 (s), 29.89 (s), 29.79 (s), 27.82 (s), 27.80 (s), 25.57 (s), 23.35 (s), 14.37 (s). $\delta_F(CD_3OD/CDCl_3$, 2/1): −196.35 (1F, m). $\delta_P(CD_3OD/CDCl_3$, 2/1): 2.145 (s). MS (CI) *m/z* 437.2 ($M^+ + 1 - 2Na^+$, 86.37). HRMS for $C_{21}H_{39}FO_6P$ ($M^+ + 1 - 2Na^+$): found 437.2429, calcd 437.2390. $[\alpha]^{20}_D$ +0.57° (*c* 0.58, MeOH). The compound was converted to the sodium salt by ion exchange and stored in solid form at −80 °C as described for **1a**.

1-Phospho-2(*S*)-fluorine-3-palmitoyl-propane-1,3-diol (**2b**) was obtained similarly as above as a white solid in 91% yield. $\delta_H(D_2O/CD_3OD)$: 4.81 (dm, J = 48.8 Hz, 1H), 4.24 (dd, J = 7.6, 6.4 Hz, 2H), 3.87 (dm, J = 5.7 Hz, 2H), 2.27 (t, J = 5.2 Hz, 2H), 1.49 (m, 2H), 1.16 (m, 24H), 0.76 (t, J = 6.0 Hz, 3H). $\delta_C(D_2O/CD_3OD)$: 173.43 (s), 88.57 (dd, J = 178.7, 7.6 Hz), 65.87 (dd, J = 23.8, 5.4 Hz), 61.92 (d, J = 23.8 Hz), 33.77 (s), 31.72 (s), 29.49 (s), 29.45 (s), 29.39 (s), 29.25 (s), 29.16 (s), 29.03 (s), 28.89 (s), 24.62 (s), 22.48 (s), 13.87 (s). $\delta_F(D_2O/CD_3OD)$: −194.87 (1F, m). $\delta_P(D_2O/CD_3OD)$: 4.325 (s). MS (CI) *m/z* 441.4 ($M^+ + 1 - 2Na^+$, 100.00). HRMS for $C_{19}H_{43}FO_6P$ ($M^+ + 1$): found 411.2307, calcd 411.2312. $[\alpha]^{20}_D$ −5.00° (*c* 0.08, MeOH/H_2O, 1/1, v/v). The compound was converted to the sodium salt by ion exchange and stored in solid form at −80 °C as described for **1a**.

1-Phospho-2(*R*)-fluorine-3-oleoyl-propane-1,3-diol (**2c**) was obtained similarly as above as a white solid. $[\alpha]^{20}_D$ −0.69° (*c* 0.45, MeOH). The compound was converted to the sodium salt by ion exchange and stored in solid form at −80 °C as described for **1a**.

1-Phospho-2(*R*)-fluorine-3-palmitoyl-propane-1,3-diol (**2d**) was obtained similarly as a white solid. $[\alpha]^{20}_D$ −4.51° (*c* 0.24, MeOH/H_2O 1/1, v/v). The compound was converted to the sodium salt by ion exchange and stored in solid form at −80 °C as described for **1a**.

Diethyl [1-Fluoro-3,4-epoxy-butyl]phosphonate (**22).** K_2CO_3 (0.375 g, 2.71 mmol) was added to a solution of iodohydrin **21** (0.160 g, 0.452 mmol) in MeOH (20 mL). The reaction mixture was stirred for 10 min at room temperature, diluted with water, and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give 69 mg. (0.307 mmol, 68%, *n*-hexanes:ethyl acetate 1:2, R_f 0.21) of epoxide **22** as a colorless liquid. $\delta_H(CDCl_3)$: 4.94−4.70 (m, 1H), 4.18−4.09 (m, 4H), 3.09 (m, 1H), 2.79 (t, J = 4.8 Hz, 0.5H), 2.72 (t, J = 4.4 Hz, 0.5H), 2.50 (m, 1H), 2.21−2.08 (m, 2H), 1.28 (m, 6H). $\delta_C(CDCl_3)$: 86.85 (dd, J = 172. 6, 148.0 Hz), 86.32 (dd, J = 172. 6, 148.0 Hz), 63.24 (dd, J = 7.6, 3.8 Hz), 62.88 (dd, J = 10.8, 6.1 Hz), 48.40 (dd, J = 14.6, 3.8 Hz), 48.17 (dd, J = 16. 9, 3.8 Hz), 47.54 (s), 46.32 (s), 33.73 (dd, J = 20.6, 1.5 Hz), 32.79 (dd, J = 19.9, 1.5 Hz), 16.33 (d, J = 3.0 Hz), 16.27 (d, J = 3.1 Hz). $\delta_F(CDCl_3)$: −207.82 (0.5F, m), −211.22 (0.5F, m). $\delta_P(CDCl_3)$: 18.02 (0.5d, J = 73.8 Hz), 17.97 (0.5d, J = 75.0 Hz). MS (CI) *m/z* 227.1 ($M^+ + 1$, 15.81), 203.1 ($M^+ + 1$, 11.28). HRMS for $C_8H_{17}FO_4P$ ($M^+ + 1$): found 227.0836, calcd 227.0849.

Hydrolytic Kinetic Resolution of Epoxide 22. A 10-mL flask equipped with a stir bar was charged with (*R,R*)-**23** (26.7 mg, 43 μmol, 0.01 equiv). The catalyst was dissolved in 0.4 mL of PhMe and treated with AcOH (10 μL, 0.177 mmol). The solution was allowed to stir at room temperature open to air for 30 min; the color changed from orange-red to a dark brown. The solution was concentrated in vacuo to leave a crude brown solid. The resulting catalyst residue was dissolved in a solution of epoxide **22** (1.00 g, 4.425 mmol) and THF (150 μL) at room temperature, the reaction flask was cooled to 0 °C, and H_2O (36 μL, 1.991 mmol, 0.45 equiv) was added dropwise over 5 min. The reaction was allowed to warm to room temperature with stirring for 14 h. The reaction mixture was diluted with 20 mL of CH_2Cl_2 and the precipitate was removed by passage through Celite 351. Flash chromatography on silica gel afforded (*R*)-epoxide **25a** (0.485 g, 2.146 mmol, 97%, R_f 0.32, CH_2Cl_2:CH_3OH 20:1) and (*S*)-diol **24a** (0.394 g, 1.615 mmol, 73%, R_f 0.34, CH_2Cl_2:CH_3OH 10:1). The ee value of **24a** was 91%, which is obtained by conversion to the known[25] isopropylidene-protected ketal. A comparison of the reported optical rotation values was then made.

Diethyl [1-Fluoro-3(*S*)-4-dihydroxybutyl]phosphonate (**24a**) was obtained as described above as a colorless liquid. $\delta_H(CDCl_3)$: 5.13−4.88 (m, 1H), 4.21−4.05 (m, 4H), 3.97−3.85 (br, 2H), 3.61−3.41 (m, 3H), 2.12−1.94 (m, 2H), 1.31 (m, 6H). $\delta_C(CDCl_3)$: 86.16 (dd, J = 171.0, 180.0 Hz), 85.54 (dd, J = 171.0, 180.0 Hz), 68.34 (dd, J = 9.3, 3.1 Hz), 67.23 (dd, J = 14.2, 1.8 Hz), 66.59 (s), 65.88 (s), 63.65 (d, J = 7.6 Hz), 63.44 (d, J = 6.8 Hz), 63.19 (d, J = 6.9 Hz), 63.12 (d, J = 6.1 Hz), 33.87 (d, J = 20.0 Hz), 33.68 (d, J = 19.1 Hz), 16.34 (d, J = 5.3 Hz), 16.29 (d, J = 4.6 Hz). $\delta_F(CDCl_3)$: −207.48 (0.5F, m), −211.53 (0.5F, m). $\delta_P(CDCl_3)$: 19.91 (0.5P, d, J = 75.0 Hz), 19.40 (0.5P, d, J = 76.1 Hz). MS (CI) *m/z* 245.2 ($M^+ + 1$, 100.00), 231.1 ($M^+ + 2 - CH_3$, 3.27). HRMS for $C_8H_{19}FO_5P$ ($M^+ + 1$): found 245.0965, calcd 245.0954. $[\alpha]^{20}_D$ −18.77 (*c* 3.08, MeOH).

Diethyl [1-Difluoro-3(*R*)-3,4-epoxy-butyl]phosphonate (25a). 25a was recovered in resolved form as described above as a colorless liquid. $\delta_C(CDCl_3)$: 4.97−4.72 (m, 1H), 4.21−4.12 (m, 4H), 3.14−3.10 (m, 1H), 2.83 (t, J = 4.0 Hz, 0.5H), 2.75 (t, J = 4.0 Hz, 0.5H), 2.54 (m, 1H), 2.29−2.08 (m, 2H), 1.32 (m, 6H). $\delta_C(CDCl_3)$: 85.92 (dd, J = 180.9, 172.5 Hz), 86.17 (dd, J = 180.2, 172. 6 Hz), 63.35 (d, J = 3.1 Hz), 63.28 (d, J = 3.1 Hz), 63.00 (d, J = 4.6 Hz), 62.93 (d, J = 4.6 Hz), 48.49 (dd, J

= 14.6, 3.8 Hz), 48.26 (dd, J = 17.6, 3.8 Hz), 47.63 (s), 46.41 (s), 37.80 (d, J = 19.8 Hz), 32.85 (d, J = 19.9 Hz), 16.40 (d, J = 12.4 Hz), 16.35 (d, J = 12.0 Hz). δ_F($CDCl_3$): −207.73 (0.5F, m), −211.17 (0.5F, m). δ_P($CDCl_3$): 18.07 (d, J = 73.8 Hz). $[\alpha]^{20}_D$ +9.75 (*c* 3.54, MeOH).

To obtain the enantiomeric diol **24b**, the enantiomeric catalyst was employed as follows. A 10-mL flask equipped with a stir bar was charged with (*S*,*S*)-**23** (20.3 mg, 34 μmol, 0.01 equiv). The catalyst was dissolved in 0.4 mL of PhMe and treated with AcOH (7 μL, 0.134 mmol). The solution was allowed to stir at room temperature open to air for 30 min; the color changed from orange-red to a dark brown. The solution was concentrated in vacuo to leave a crude brown solid. The resulting catalyst residue was dissolved in epoxide (0.758 g, 3.35 mmol) and THF (120 μL) at room temperature, the reaction flask was cooled to 0 °C, and H_2O (27 μL, 1.51 mmol, 0.45 equiv) was added dropwise over 5 min. The reaction was allowed to warm to room temperature, stirred for 14 h, concentrated, and purified on silica gel to give (*S*)-epoxide **25b** (0.369 g, 1.63 mmol, 98%) and (*S*)-diol **24b** (0.375 g, 1.54 mmol, 90%). The ee value of diol **24b** was 89%, obtained by conversion of **24b** to the known[25] ketal and comparison of the reported optical rotations.

Diethyl [1-fluoro-3(*R*)-4-dihydroxybutyl]phosphonate (24b) was obtained as above as a colorless liquid. δ_H($CDCl_3$): 4.97−4.72 (m, 1H), 4.21−4.12 (m, 4H), 3.14−3.10 (m, 1H), 2.83 (t, J = 4.0 Hz, 0.5H), 2.75 (t, J = 4.0 Hz, 0.5H), 2.54 (m, 1H), 2.29−2.08 (m, 2H), 1.32 (m, 6H). δ_C($CDCl_3$): 86.17 (dd, J = 180.2, 172. 6 Hz), 85.92 (dd, J = 180.9, 172.5 Hz), 63.35 (d, J = 3.1 Hz), 63.28 (d, J = 3.1 Hz), 63.00 (d, J = 4.6 Hz), 62.93 (d, J = 4.6 Hz), 48.49 (dd, J = 14.6, 3.8 Hz), 48.26 (dd, J = 17.6, 3.8 Hz), 47.63 (s), 46.41 (s), 37.80 (d, J = 19.8 Hz), 32.85 (d, J = 19.9 Hz), 16.40 (d, J = 12.4 Hz), 16.35 (d, J = 12.0 Hz). δ_F($CDCl_3$): −207.73 (0.5F, m), −211.17 (0.5F, m). δ_P($CDCl_3$): 19.91 (0.5P, d, J = 75.0 Hz), 19.40 (0.5P, d, J = 76.1 Hz). $[\alpha]^{20}_D$ +16.30 (*c* 4.50, MeOH).

Diethyl [1-difluoro-3(*S*)-3,4-epoxy-butyl]phosphonate (**25b**) was recovered in resolved form as a colorless liquid. δ_H($CDCl_3$): 4.97−4.72 (m, 1H), 4.21−4.12 (m, 4H), 3.14−3.10 (m, 1H), 2.83 (t, J = 4.0 Hz, 0.5H), 2.75 (t, J = 4.0 Hz, 0.5H), 2.54 (m, 1H), 2.29−2.08 (m, 2H), 1.32 (m, 6H). δ_C($CDCl_3$): 85.92 (dd, J = 180.9, 172.5 Hz), 86.17 (dd, J = 180.2, 172. 6 Hz), 63.35 (d, J = 3.1 Hz), 63.28 (d, J = 3.1 Hz), 63.00 (d, J = 4.6 Hz), 62.93 (d, J = 4.6 Hz), 48.49 (dd, J = 14.6, 3.8 Hz), 48.26 (dd, J = 17.6, 3.8 Hz), 47.63 (s), 46.41 (s), 37.80 (d, J = 19.8 Hz), 32.85 (d, J = 19.9 Hz), 16.40 (d, J = 12.4 Hz), 16.35 (d, J = 12.0 Hz). δ_F($CDCl_3$): −207.73 (0.5F, m), −211.17 (0.5F, m). δ_P($CDCl_3$): 18.07 (d, J = 73.8 Hz). $[\alpha]^{20}_D$ +12.06 (*c* 2.33, MeOH).

Diethyl [1-Fluoro-3(*S*)-hydroxyl-4-(oleoyloxy)butyl]-phosphonate (26aa). To a solution of diol **24a** (107 mg, 0.438 mmol) and oleic acid (118 mg, 0.416 mmol) in dry CH_2Cl_2 (2 mL) was added a solution of DCC (109 mg, 0.526 mmol) and DMAP (32 mg, 0.263 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C. The solution was stirred for 16 h at 0 °C, filtered, concentrated in vacuo, and the residue was purified on silica gel (*n*-hexanes−ethyl acetate, HE:AE 1:1, R_f 0.29) to afford ester (121 mg, 0.238 mmol, 51%) as a waxy solid. δ_H($CDCl_3$): 5.29 (m, 2H), 5.10−4.89 (m, 1H), 4.22−3.98 (m, 7H), 3.48 (br, 1H), 2.29 (t, J = 7.6 Hz, 2H), 2.18−2.03 (m, 2H), 1.93 (m, 4H), 1.58 (m, 2H), 1.33−1.22 (m, 28H), 0.83 (t, J = 7.2 Hz, 3H). δ_C($CDCl_3$): 173.84 (s), 173.81 (s), 129.92 (s), 129.64 (s), 86.49 (dd, J = 171.0, 172.6 Hz), 84.71 (dd, J = 171.1, 172.6 Hz), 68.06 (s), 67.48 (s), 66.01 (dd, J = 10.0, 3.8 Hz), 65.07 (dd, J = 13.1, 3.0 Hz), 63.55 (d, J = 6.9 Hz), 63.30 (d, J = 6.9 Hz), 63.06 (d, J = 6.9 Hz), 62.98 (d, J = 8.4 Hz), 34.36 (d, J = 19.9 Hz), 33.81 (d, J = 18.4 Hz), 31.82 (s), 29.67 (s), 29.61 (s), 29.43 (s), 29.23 (s), 29.09 (s), 27.13 (s), 27.08 (s), 24.86 (s), 22.59 (s), 16.35 (m), 14.02 (s). δ_F($CDCl_3$): −208.26 (0.5F, m), −211.75 (0.5F, m). δ_P($CDCl_3$): 19.36 (0.5P, d, J = 73.8 Hz), 19.10 (0.5P, d, J = 76.1 Hz). MS (CI) *m*/*z* 509.4 (M^+ + 1, 29.75), 463.3 (M^+ − OC_2H_5, 100.00). HRMS for $C_{26}H_{51}FO_6P$ (M^+ + 1): found 509.3400, calcd 509.3407. $[\alpha]^{20}_D$ −2.61 (*c* 2.38, MeOH).

Diethyl[1-fluoro-3(*S*)-hydroxyl-4-(palmitoyloxy)butyl]-phosphonate (**26ab**) was obtained similarly as above as a white solid, 51% yield. δ_H($CDCl_3$): 5.11−4.90 (m, 1H), 4.23−3.99 (m, 7H), 3.42 (br, 1H), 2.31 (t, J = 7.6 Hz, 2H), 2.19−1.90 (m, 2H), 1.68−1.55 (m, 2H), 1.33 (t, J = 6.8 Hz, 6H), 1.60 (m, 24H), 0.84 (t, J = 7.2 Hz, 3H). δ_C($CDCl_3$): 173.92 (s), 173.89 (s), 86.56 (dd, J = 171.0, 168.2 Hz), 84.78 (dd, J = 171.0, 168.2 Hz), 68.10 (s), 67.53 (s), 66.11 (dd, J = 9.3, 3.8 Hz), 65.21 (dd, J = 13.0, 3.1 Hz), 63.48 (dd, J = 24.6, 6.9 Hz), 63.05 (dd, J = 9.3, 6.8 Hz), 49.03 (s), 34.36 (d, J = 19.9 Hz), 31.87 (s), 29.63 (s), 29.60 (s), 29.41 (s), 29.22 (s), 29.09 (s), 25.59 (s), 24.86 (s), 22.63 (s), 16.41 (d, J = 5.3 Hz), 16.37 (d, J = 4.6 Hz), 14.06 (s). δ_F($CDCl_3$): −208.37 (0.5F, m), −211.62 (0.5F, m). δ_P($CDCl_3$): 19.34 (0.5P, d, J = 73.8 Hz), 19.11 (0.5P, d, J = 76.1 Hz). MS (CI) *m*/*z* 483.4 (M^+ + 1, 55.29), 437.4 (M^+ − OC_2H_5, 100.00). HRMS for $C_{24}H_{49}FO_6P$ (M^+ + 1): found 483.3244, calcd 483.3251. $[\alpha]^{20}_D$ −2.20 (*c* 1.00, MeOH).

[1-Fluoro-3(*S*)-hydroxyl-4-(oleoyloxy)butyl]phosphonate (3aa). Thoroughly dried precursor **26aa** (117 mg, 0.203 mmol, 5 h under high vacuum) was dissolved in dry methylene chloride (1 mL) at room temperature, bromotrimethylsilane (353 mg, 2.03 mmol) was added with a dry syringe, and the mixture was stirred for 4 h. When TLC indicated that all of the reactant had been consumed, the solvents were removed in vacuo. The residue was dissolved in 95% methanol (1 mL) for 1 h and reconcentrated in vacuo to give a final product (88 mg, 0.195 mmol, 96% yield) of phosphonate **3aa**. δ_H(CD_3OD): 5.34 (m, 2H), 5.21−5.17 (m, 1H), 4.79 (m, 1H), 3.68 (dd, J = 11.60, 4.40 Hz, 1H), 3.57 (m, 1H), 2.35 (m, 4H), 2.01 (m, 4H), 1.63 (m, 2H), 1.33−1.22 (m, 20H), 0.89 (t, J = 7.2 Hz, 3H). δ_C($CDCl_3$): 174.33 (s), 174.17 (s), 130.84 (s), 130.74 (s), 88.16 (dd, J = 170.3, 168.7 Hz), 86.39 (dd, J = 170.3, 168.7 Hz), 71.30 (dd, J = 14.6, 2.3 Hz), 69.52 (dd, J = 14.6, 2.3 Hz), 35.12 (d, J = 19.3 Hz), 34.93 (d, J = 18.9 Hz), 33.04 (s), 30.84 (s), 30.77 (s), 30.61 (s), 30.44 (s), 30.35 (s), 30.26 (s), 30.16 (s), 30.13 (s), 28.14 (s), 28.13 (s), 23.72 (s), 14.55 (s). δ_F($CDCl_3$): −208.60 (0.5F, m), −210.99 (0.5F, m). δ_P($CDCl_3$): 16.21 (0.5P, d, J = 72.7 Hz), 15.95 (0.5P, d, J = 73.8 Hz). MS (CI) *m*/*z* 435.3 (M^+ − OH, 60.85), 283.3 (M^+ − C_4H_9 − CFH_3PO_3, 100.00). HRMS for $C_{22}H_{41}FO_5P$ (M^+ − OH): found 435.2678, calcd 435.2676. $[\alpha]^{20}_D$ −2.13 (*c* 0.14, MeOH). The compound was converted to the sodium salt by ion exchange and stored in solid form at −80 °C as described for **1a**.

[1-Fluoro-3(*S*)-hydroxyl-4-(palmitoyloxy)butyl]phosphonate (**3ab**) was obtained similarly from precursor **26ab** in 91% yield. δ_H(CD_3OD): 5.27−5.18 (m, 1H), 4.78 (m, 1H), 3.68 (dd, J = 10.80, 4.00 Hz, 1H), 3.57 (m, 1H), 2.40−2.25 (m, 4H), 1.64 (m, 2H), 1.33−1.22 (m, 24H), 0.89 (t, J = 7.2 Hz, 3H). δ_C($CDCl_3$): 172.33 (s), 172.30 (s), 87.06 (dd, J = 170.3, 168.7 Hz), 85.29 (dd, J = 170.3, 168.7 Hz), 69.33 (dd, J = 14.2, 2.4 Hz), 67.56 (dd, J = 14.2, 2.4 Hz), 33.04 (d, J = 7.7 Hz), 31.92 (s), 31.06 (s), 28.77 (s), 28.75 (s), 28.71 (s), 28.58 (s), 28.47 (s), 28.39 (s), 28.15 (s), 24.05 (s), 23.97 (s), 23.92 (s), 21.72 (s), 12.48 (s). δ_F($CDCl_3$): −208.73 (0.5F, m), −211.07 (0.5F, m). δ_P($CDCl_3$): 16.21 (0.5P, d, J = 72.7 Hz), 15.95 (0.5P, d, J = 73.8 Hz). MS (CI) *m*/*z* 409.2 (M^+ + 1 − OH − CH_3, 2.29), 225.2 (M^+ − $C_{14}H_{29}$ − OH, 100.00). HRMS for $C_{20}H_{38}FO_5P$ (M^+ − OH − CH_3): found 408.2432, calcd 408.2441. $[\alpha]^{20}_D$ −1.83 (*c* 0.17, MeOH). The compound was converted to the sodium salt by ion exchange and stored in solid form at −80 °C as described for **1a**.

Diethyl [1-fluoro-3(*R*)-hydroxyl-4-(oleoyloxy)butyl]-phosphonate (**26ba**) was obtained as a waxy solid in 56% yield. δ_H($CDCl_3$): 5.29 (m, 2H), 5.10−4.90 (m, 1H), 4.22−3.98 (m, 7H), 3.44 (br, 1H), 2.30 (t, J = 7.6 Hz, 2H), 2.18−2.03 (m, 2H), 1.93 (m, 4H), 1.56 (m, 2H), 1.33−1.22 (m, 28H), 0.83 (t, J = 7.2 Hz, 3H). δ_C($CDCl_3$): 173.84 (s), 173.81 (s), 129.92 (s), 129.64 (s), 86.49 (dd, J = 171.0, 172.6 Hz), 84.71 (dd, J = 171.1, 172.6 Hz), 68.06 (s), 67.48 (s), 66.01 (dd, J = 10.0, 3.8 Hz), 65.07 (dd, J = 13.1, 3.0 Hz), 63.55 (d, J = 7.0 Hz), 63.30 (d, J

= 7.0 Hz), 63.06 (d, J = 7.0 Hz), 62.98 (d, J = 8.4 Hz), 34.36 (d, J = 19.9 Hz), 33.81 (d, J = 18.4 Hz), 31.82 (s), 29.67 (s), 29.61 (s), 29.43 (s), 29.23 (s), 29.09 (s), 27.13 (s), 27.08 (s), 24.86 (s), 22.59 (s), 16.35 (m), 14.02 (s). δ_F($CDCl_3$): −208.29 (0.5F, m), −211.75 (0.5F, m). δ_P($CDCl_3$): 19.36 (0.5P, d, J = 73.8 Hz), 19.10 (0.5P, d, J = 76.1 Hz). $[\alpha]^{20}_D$ +2.47 (*c* 1.86, MeOH).

Diethyl[1-fluoro-3(*R*)-hydroxyl-4-(palmitoyloxy)butyl]-phosphonate (**26bb**) was obtained as a white solid in 53% yield. δ_H($CDCl_3$): 5.11−4.90 (m, 1H), 4.20−3.99 (m, 7H), 3.42 (br, 1H), 2.29 (t, J = 7.6 Hz, 2H), 2.19−1.90 (m, 2H), 1.58 (t, J = 6.8 Hz, 2H), 1.33 (t, J = 6.8 Hz, 6H), 1.60 (m, 24H), 0.83 (t, J = 7.2 Hz, 3H). δ_C($CDCl_3$): 173.88 (s), 173.85 (s), 86.00 (dd, J = 178.7, 171.1 Hz), 85.23 (dd, J = 178.7, 171.1 Hz), 68.06 (s), 67.50 (s), 66.05 (dd, J = 10.1, 4.6 Hz), 65.08 (dd, J = 10.1, 4.6 Hz), 63.44 (dd, J = 25.3, 7.6 Hz), 63.04 (dd, J = 6.8, 6.8 Hz), 34.37 (d, J = 19.9 Hz), 31.85 (s), 29.61 (s), 29.57 (s), 29.53 (s), 29.38 (s), 29.28 (s), 29.19 (s), 29.07 (s), 22.61 (s), 16.38 (d, J = 5.3 Hz), 16.34 (d, J = 4.6 Hz), 14.03 (s). δ_F($CDCl_3$): −208.28 (0.5F, m), −211.75 (0.5F, m). δ_P($CDCl_3$): 19.37 (0.5P, d, J = 73.8 Hz), 19.10 (0.5P, d, J = 76.1 Hz). $[\alpha]^{20}_D$ +3.01 (*c* 0.84, MeOH).

[1-Fluoro-3(*R*)-hydroxyl-4-(oleoyloxy)butyl]phosphonate (**3ba**) was obtained in 94% yield from precursor **26ba**. δ_H(CD_3OD): 5.34 (m, 2H), 5.33−5.17 (m, 1H), 4.79 (m, 1H), 3.68 (dd, J = 11.60, 4.40 Hz, 1H), 3.59 (m, 1H), 2.35 (m, 4H), 2.02 (m, 4H), 1.61 (m, 2H), 1.33−1.22 (m, 20H), 0.89 (t, J = 7.2 Hz, 3H). δ_C($CDCl_3$): 174.38 (s), 174.22 (s), 130.84 (s), 130.74 (s), 88.16 (dd, J = 170.25, 168.74 Hz), 86.39 (dd, J = 170.25, 168.74 Hz), 71.30 (dd, J = 14.58, 2.31 Hz), 69.52 (dd, J = 14.58, 2.31 Hz), 35.12 (d, J = 19.32 Hz), 34.93 (d, J = 18.89 Hz), 33.04 (s), 30.84 (s), 30.77 (s), 30.61 (s), 30.44 (s), 30.35 (s), 30.26 (s), 30.16 (s), 30.13 (s), 28.14 (s), 28.13 (s), 23.72 (s), 14.55 (s). δ_F($CDCl_3$): −208.68 (0.5F, m), −210.99 (0.5F, m). δ_P($CDCl_3$): 16.01 (0.5P, d, J = 72.86 Hz), 15.93 (0.5P, d, J = 74.00 Hz). $[\alpha]^{20}_D$ +2.01 (*c* 0.22, MeOH). The compound was converted to the sodium salt by ion exchange and stored in solid form at −80 °C as described for **1a**.

[1-Fluoro-3(*R*)-hydroxyl-4-(palmitoyloxy)butyl]phosphonate (**3bb**) was obtained in 88% yield from precursor **26bb**. δ_H(CD_3OD): 5.27−5.18 (m, 1H), 4.78 (m, 1H), 3.68 (dd, J = 10.80, 4.00 Hz, 1H), 3.57 (m, 1H), 2.40−2.25 (m, 4H), 1.64 (m, 2H), 1.33−1.22 (m, 24H), 0.89 (t, J = 7.2 Hz, 3H). δ_C($CDCl_3$): 172.33 (s), 172.30 (s), 87.06 (dd, J = 170.25, 168.74 Hz), 85.29 (dd, J = 170.25, 168.74 Hz), 69.33 (dd, J = 14.21, 2.35 Hz), 67.56 (dd, J = 14.21, 2.35 Hz), 33.04 (d, J = 7.68 Hz), 31.92 (s), 31.06 (s), 28.77 (s), 28.75 (s), 28.71 (s), 28.58 (s), 28.47 (s), 28.39 (s), 28.15 (s), 24.05 (s), 23.97 (s), 23.92 (s), 21.72 (s), 12.48 (s). δ_F($CDCl_3$): −208.73 (0.5F, m), −211.07 (0.5F, m). δ_P($CDCl_3$): 16.19 (0.5P, d, J = 72.70 Hz), 15.84 (0.5P, d, J = 73.84 Hz). $[\alpha]^{20}_D$ +2.56 (*c* 0.13, MeOH). The compound was converted to the sodium salt by ion exchange and stored in solid form at −80 °C as described for **1a**.

1-Diethylphosphonyl-3,4-*O*-isopropylidene-1(*R*,*S*)-3(*S*),4-butanetriol (29). To a solution of diethyl phosphite (3.80 g, 24.1 mmol) in 8 mL of THF at −78 °C was added lithium bis-(trimethylsilyl)amide (24.1 mL, 1.0 M) in THF. The solution was allowed to warm to room temperature and stirred for 45 min, and then cooled to −20 °C. Aldehyde **28** (3.3 g, 22.92 mmol) in 20 mL of THF was transferred into the solution at this temperature. The reaction mixture was allowed to warm to room temperature slowly and stirred overnight and then quenched by slow addition of acetic acid (24.1 mmol, 1.39 mL) in 10 mL of ether. The organics were filtered through Celite, which were then washed with ethyl acetate. The solvents were removed in vacuo to give a colorless oil that was purified by flash chromatography to afford the phosphonate **29**. ^{1}H, ^{13}C, ^{31}P NMR are identical with those reported.[50]

1-Diethylphosphonyl-1-fluorine-3,4-*O*-isopropylidene-1(*R*,*S*)-3(*S*),4-butanetriol (**30**) was prepared by DAST fluorination following the procedure described for compound **16**. δ_H($CDCl_3$): 4.70−5.01 (m, 1H), 4.04−4.35 (m, 6H), 3.54−3.66 (m, 1H), 1.90−2.28 (m, 2H), 1.30−1.38 (m, 12H). δ_P ($CDCl_3$), 18.65 (d, J = 73.84 Hz, integration, 91.42), 18.36 (d, J = 76.10 Hz, integration, 8.58). δ_F($CDCl_3$): −207.52 (0.085F, m), −212.52 (0.915F, m).[25]

Platelet Activation Assays. Selected compounds were tested at a concentration of 1 μM for their ability to activate gel-filtered platelets (~300 000 platelets/μL in 129 mM NaCl, 9.9 mM $NaHCO_3$, 2.8 mM KCl, 0.8 mM KH_2PO_4, 5.6 mM dextrose, 10 mM HEPES, 2 mM $CaCl_2$, 1 mM $MgCl_2$) in the presence of fibrinogen (100 μg/mL), using a dual channel aggregometer (Chronolog; Haverton, PA) as previously described.[53]

PPARγ Activation Assays.[5] RAW 264.7 monocytic cells were transfected with rat acyl-CoA oxidase PPRE-luciferase and SV40 β-galactosidase reporter plasmids, and treated with 5 μM *sn*-1-*O*-oleoyl LPA (Avanti Polar Lipids, Alabaster, AL) or with 5 μM of each of the four *sn*-1 or *sn*-2-monofluoro analogues of LPA for 16 h. Then, relative amounts of luciferase and β-galactosidase were determined. Data are shown as relative light units (luciferase) normalized for transfection efficiency (β-Gal).

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Supporting Information Available: ^{1}H NMR spectra of all the intermediates and the monofluorinated LPA analogues (**1, 2, 3**) described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

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