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Synthesis of α-Fluorinated Phosphonates from α-Fluorovinylphosphonates: A New Route to Analogues of Lysophosphatidic Acid

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

Department of Medicinal Chemistry, The University of Utah, 419 Wakara Way, Suite 205, Salt Lake City, Utah 84108-1257

gprestwich@pharm.utah.edu

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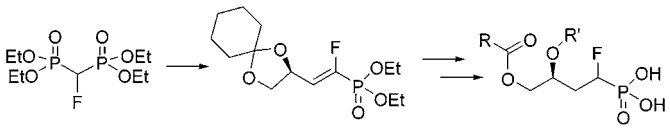
ABSTRACT



A versatile, efficient method for the preparation of α-monofluoromethylene (–CHF–) phosphonates from α-fluorovinylphosphonate provides access to a class of lysophosphatidic acid (LPA) receptor-subtype agonists. In addition, *sn*-2 *O*-methylation of α-monofluoromethylene phosphonates using trimethylsilyldiazomethane generated *sn*-1-acyl, 2-*O*-methyl α-monofluoromethylene derivatives. Finally, a novel method for the selective etherification of 1,2-diols was developed and a new class of *sn*-1 *O*-methyl, 2-acyl α-monofluoromethylene LPA analogues was prepared.

Lysophosphatidic acid (LPA, 1- or 2-acyl-*sn*-glycerol 3-phosphate) elicits a wide variety of responses from cells and tissues including calcium mobilization, changes in cell shape and mobility, mitogenesis, and anti-apoptosis. These effects are mediated via interactions with G-protein coupled receptors named LPA_1, LPA_2, and LPA_3 (formerly Edg-2, Edg-4, and Edg-7).[1−3] These receptors share 50−55% identical amino acids and cluster with five other receptors for the structurally related lipid sphingosine 1-phosphate (S1P). Assignment of a physiological response to stimulation of a particular LPA receptor is difficult because ligands that discriminate among receptor subtypes are lacking. The problem is exacerbated by the existence of at least three lipid phosphate phosphatases (LPPs), which degrade extracellular LPA, and LPA acyl transferases, which convert LPA to phosphatidic acid (PA). Thus, we have prepared a variety of new chemical entities that can act as metabolically stabilized LPA receptor subtype-selective agonists or antagonists.

One common approach for stabilization of phosphate monoesters is the use of a phosphonate analogue. Though less well-studied, recent experimental and theoretical reports have suggested that the α-fluoromethylene phosphonate groups would better mimic the phosphate than either the methylene or difluoromethylene derivatives.[4−6] Several monofluoromethylene phosphonates have been studied as potential enzyme inhibitors and as probes for the elucidation of biochemical processes.[7,8] Indeed, we have recently described the enantioselective synthesis and selected biological activi-

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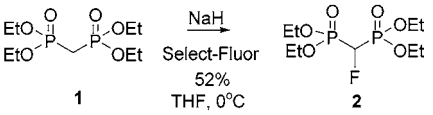
ties of a variety of fluorinated phosphate and phosphonate analogues of LPA.[9−12] The preliminary biological results have demonstrated that α-monofluorinated phosphonate mimics of LPA are unique new non-hydrolyzable ligands with surprising enantiospecific- and receptor-specific biological readouts, with one compound showing a 1000-fold higher activity relative to 1-oleoyl LPA for the LPA_3 receptor.[13]

We have recently developed two synthetic routes for the synthesis of α-monofluorinated phosphonates as LPA analogues. Encouraged by the high biological activity and potential application of these analogues, we now report a new, versatile, and efficient method for the synthesis of α-monofluorinated LPA analogues by hydrogenation of α-fluorovinylphosphonates.

In designing a new approach to the α-monofluorophosphonates that could result in diastereoselective synthesis by asymmetric hydrogenation, we selected the Wadsworth−Emmons condensation of the carbanion derived from a tetraalkyl monofluoromethylenediphosphonate with (*R*)-1,4-dioxaspiro[4,5]decane-2-carbaldehyde as the key assembly step. The cyclohexyl protecting group in the aldehyde was expected to increase the stereoselectivity of condensation, since the preferred conformation of vinylphosphonate would have the most bulky *β*-carbon substituent trans to the phosphoryl group. Although several procedures for the synthesis of tetraalkyl monofluoromethylenediphosphonates have been described, none appeared suitable for this strategy.[14,15] After evaluation a number of electrophilic fluorine donors, we found that Selectfluor (1-chloromethyl-4-fluoro-1,4-diazobicyclo[2.2.2]octane bis(tetrafluoroborate), F-TEDA-BF_4)[16,17] gave good yields of tetraethyl fluoromethylenebisphosphonate from the sodium hydride-generated enolate.

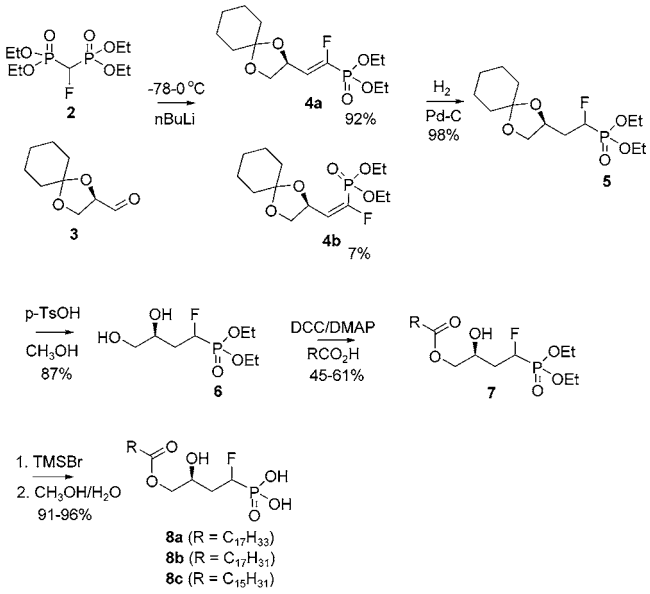
Scheme 1



Next, treatment of compound **2** with *n*-butyllithium at −78 °C generated the lithiated carbanion, which condensed smoothly with aldehyde **3** giving a good yield of the α-fluorovinylphosphonate. The condensation reaction displayed good stereoselectivity and gave a mixture of (*E*)- and (*Z*)-isomers in a 12:1 molar ratio. Moreover, these two isomers could be readily separated by flash chromatography. The stereochemistry of the major and minor isomers was assigned on the basis of the $^3J_{PH}$ and $^3J_{HF}$ coupling constants for the alkene.[18,19] The major isomer **4a** showed a small $^3J_{PH}$ coupling (7.6 Hz, δ (olefin proton) = 4.98 ppm) and could be assigned as the less-hindered *E*-isomer. The larger $^3J_{PH}$ of the minor isomer **4b** was 30.8 Hz (δ (olefin proton) = 5.41 ppm), corresponding to the *Z*-isomer. The $^3J_{HF}$ coupling constants confirmed these assignments: **4a** had $^3J_{HF}$ = 39.2 Hz, while **4b** had $^3J_{HF}$ = 26.3 Hz, consistent with trans and cis three-bond relationships, respectively.

Catalytic hydrogenation of the alkene **4** proceeded readily and quantitatively to give the corresponding diastereomeric α-fluoroalkylphosphonates **5** in a 1:1 ratio as observed by NMR. The hydrogenation was carried out at ambient temperature and pressure using 10% Pd−C in absolute ethanol. Deprotection of **5** using a catalytic amount of *p*-TsOH in MeOH was followed by carbodiimide-promoted esterification of diol **6** with palmitic, oleic, or linoleic acids to furnish good yields of esters **7a**, **7b** and **7c**, respectively. Finally, treatment of each ester **7** with bromotrimethylsilane and subsequent addition of aq. methanol (5% H_2O) provided the desired fluorinated LPA analogues **8** in nearly quantitative yield.

Scheme 2



The introduction of an *sn*-2 *O*-methyl group in LPA analogues appears to reduce the activation of LPA_2 receptors and increase the response of LPA_3 receptors.[20] Thus, OMPT, a phosphorothioate analogue of LPA (Figure 1), exhibited

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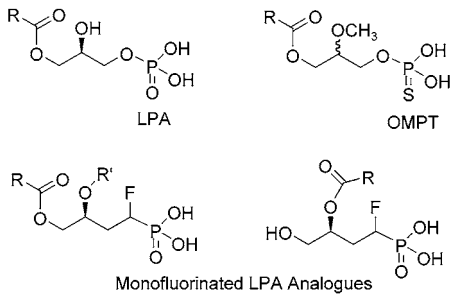
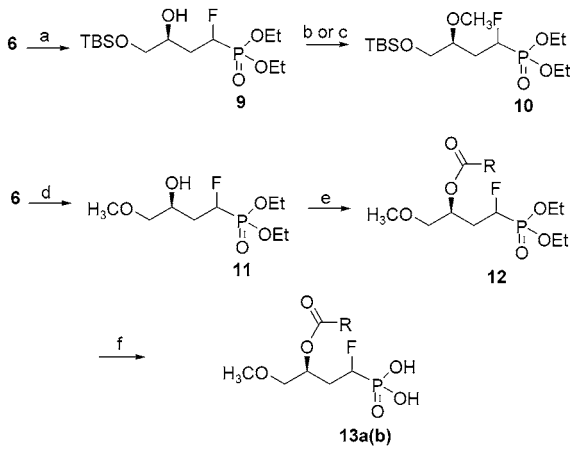


Figure 1. Monofluorinated LPA analogues.

selectivity for LPA_3 relative to LPA_1 or LPA_2. Furthermore, selective introduction of an *O*-methyl group at the *sn*-1 position could generate a novel acyl migration-blocked series of 2-acyl LPA analogues.[21] To increase the subtype selectivity of analogues **8**, methods for selective introduction of an *O*-methyl group at the *sn*-2 and *sn*-1 positions were developed.

Scheme 3[a]

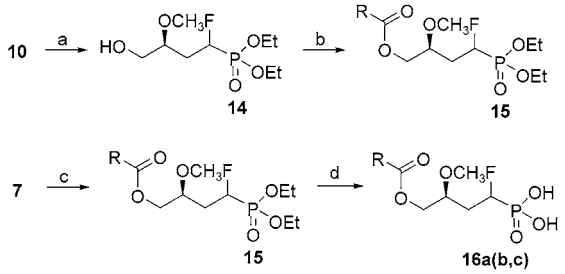


[a] Conditions: (a) TBSCl, TEA, DMAP, CH_2Cl_2, 73%; (b) $(CH_3)_3O^+BF_4^-$, Proton Sponge, 14 days, 43%; (c) $TMSCHN_2$, HBF_4, 2 h, 67%; (d) $(CH_3)_3O^+BF_4^-$, Proton Sponge, 4 days, 46%; (e) RCO_2H, DCC/DMAP, 80−92%; (f) TMSBr; CH_3OH/H_2O, 95−97%.

First, selective protection of the *sn*-1 hydroxyl as the *tert*-butyldimethylsilyl (TBS) ether was achieved using 1.05 equiv of TBS-Cl. However, the *O*-methylation of chiral secondary alcohol in the presence of the fluoromethylene phosphonate required mild conditions. Several common methods of effecting alcohol alkylation were found to be inappropriate to meet our needs.[22,23] Moreover, the γ-hydroxy-α-fluoro phosphonate is base sensitive, and the α C-H is readily deprotonated even by weak bases. Attempts to prepare the *O*-methyl derivative using sodium hydride or sodium ethoxide resulted in its decomposition. The alternate Purdie procedure using silver oxide or silver carbonate proved ineffective due to the steric hindrance.[24] Meerwein's trimethyloxonium tetrafluoroborate salts, $(CH_3)_3O^+BF_4^-$, in conjunction with non-nucleophilic amine base (e.g., Proton Sponge, 1,8-bis(dimethylamino)naphthalene) gave a modest yield (43%) of methyl ether after 14 days, together with unreacted starting material.[25] In contrast, the slow reaction could provide good regioselectivity; thus, the reaction of $(CH_3)_3O^+BF_4^-$ with diol **6** in the presence of proton sponge provided a good yield of 1-*O*-methylation product **11** after 4 days reaction at room temperature. After esterification at *sn*-2 position and deprotection of diethyl ester, the acyl-chain migration-blocked *sn*-2 LPA analogues **13** were obtained.

Diazomethane is known to react with alcohols in the presence of catalytic amounts of concentrated HBF_4 to give methyl ethers.[26] However, this method can be both tedious and dangerous. More than 10 years ago, Aoyama reported that trimethylsilyldiazomethane ($TMSCHN_2$) was a convenient reagent for the *O*-methylation of alcohols.[27] Since this *O*-methylation occurred in acidic conditions (48% aq fluoroboric acid, HBF_4), it should also be feasible for substrate **9**. In the event, we found that $TMSCHN_2$ reacted smoothly with alcohol **9** in dichloromethane in the presence of aq HBF_4 to give the corresponding methyl ether in good yield. The TBS ether was unaffected and was then deprotected with tetra(*n*-butyl)ammonium fluoride (TBAF) in THF to give the primary alcohol; neutralization of TBAF with acetic acid inhibited the side-effect of basic medium. DCC-promoted esterification of **9** with either oleic or palmitic acid provided good yields of the corresponding esters. Finally, treatment of each ester with bromotrimethylsilane and subsequent addition of 5% aq methanol provided the desired *sn*-2 *O*-methylated LPA analogues **16** in nearly quantitatively yield. Importantly, the excess TMSBr did not affect the *O*-methyl ether.

Scheme 4[a]



[a] Conditions: (a) TBAF, HOAc, THF, 93%; (b) RCO_2H, DCC/DMAP, 83−91%; (c) $TMSCHN_2$, HBF_4, 86−88%; (d) TMSBr; CH_3OH/H_2O, 95−97%.

The smooth reaction of $TMSCHN_2$ with alcohol **9** encouraged us to attempt direct etherification of acylated phospho-

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nate **7** to produce **15**. Current methods for the preparation of *sn*-2 *O*-methylated LPA analogues involved selective protection of *sn*-1 and *sn*-3 hydroxyl, introduction of an *sn*-2 *O*-methyl group under strong basic conditions, and finally construction of the LPA backbone by selective deprotection, phosphorylation, and esterification.[20,28] In the method described herein, reaction of $TMSCHN_2$ with alcohol **7** provided good yields of **15** with no acyl migration observed. This method saves several steps for the synthesis of *sn*-2 *O*-methylation LPA analogues and provides a new and concise synthetic route for the construction of this class of compounds.

In summary, we have described general, efficient methods for the preparation of α-monofluoromethylene phosphonates and of *sn*-1 and *sn*-2 *O*-methylated LPA analogues. In addition, a novel method for the selective etherification of 1,2-diols was developed. Full descriptions of biological activity and the utility of analogues as metabolically stabilized LPA mimics will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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