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Phosphomimetic sulfonamide and sulfonamidoxy analogues of (Lyso)phosphatidic acid

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Abstract—Lysophosphatidic acid (LPA) and phosphatidic acid (PA) are potent bioactive lipid mediators of signal transduction and are inactivated by phosphatases. To obtain receptor-isoform selective ligands with neutral phosphomimetic head groups, we performed the stereoselective synthesis of LPA and PA analogues with trifluoromethanesulfonamide and trifluoromethanesulfonamidoxy moieties replacing the phosphomonoester.

1. Introduction

Lysophosphatidic acid (LPA, 1- or 2-acyl-*sn*-glycero-3-phosphate) is an important signaling lipid that elicits a variety of biological effects, including platelet aggregation, smooth muscle contraction, cell morphology, modulation and cell growth stimulation, and proliferation.[1,2] LPA binds and activates five G-protein coupled receptors (GPCRs) named LPA_1, LPA_2, LPA_3, LPA_4 and LPA_5. LPA_{1-3}, which were formerly called endothelial differentiation gene receptors (EDG)[3] whereas LPA_4 and LPA_5 are members of the purinergic cluster in the GPCR superfamily.[4,5] LPA is a naturally occurring ligand for the intracellular hormone receptor PPARγ.[6,7] The therapeutic potential for isoform-selective, metabolically-stabilized lysolipid analogues has been increasingly recognized.[8,9]

LPA is found in serum at micromolar concentrations (1–20 μM), where it is mainly produced by stimulated platelets. Elevated LPA concentrations are observed in the plasma of patients with multiple myeloma and in the ascites of patients with a variety of cancers, for which it may be a marker for tumor progression.[10,11]

Phosphatidic acid (PA) regulates phosphoinositide metabolism and plays key roles in cell growth and vesicular trafficking of proteins.[12] PA can be generated by the action of phospholipase D on phosphatidylcholine (PC) and other phospholipids, or by LPA-specific acyltransferases (LPAATs), which terminate LPA signaling. In addition, the balance between LPA and PA contributes to the regulation of membrane curvature of bilayer vesicles.[13,14]

Both LPA and PA are substrates for a family of lipid phosphate phosphatases (LPPs), which regulate the ratio between phosphate esters and their de-phosphorylated products.[15–17] As integral membrane proteins, LPPs act both inside and outside the cell[14] to hydrolyze LPA to monoacylglycerol (MAG) and PA to diacylglycerol (DAG), the latter being an important activator of protein kinase C. Our group has previously reported the synthesis of a wide range of metabolically-stabilized LPA and PA analogues,[9] in which the 3-oxygen functionality of the glyceryl backbone has been replaced

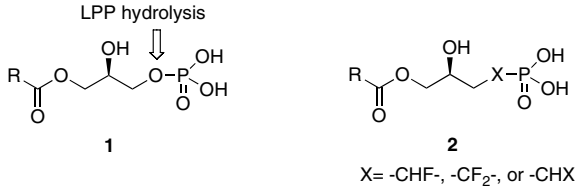

Figure 1.

Keywords: Stereoselective phospholipid synthesis; Aminooxygroup; Trifluoromethanesulfonamide; Trifluoromethanesulfonamidoxy; G-protein coupled receptor.
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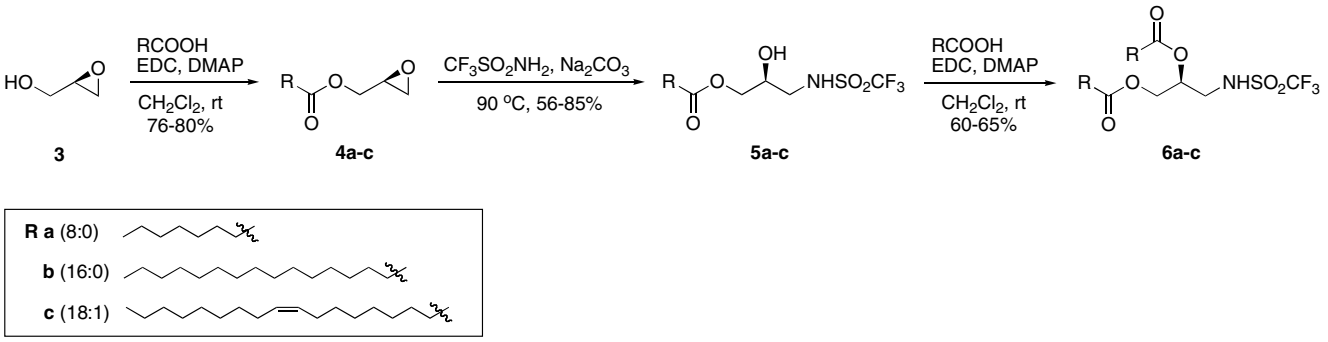


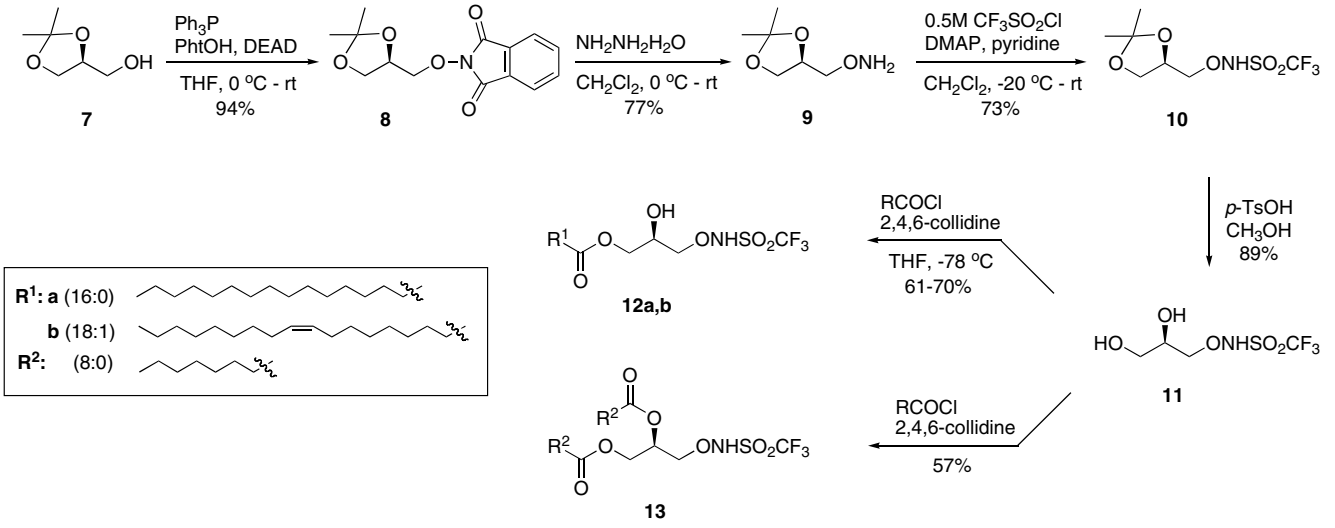
Scheme 1.

with methylene, fluoromethylene, and difluoromethylene (Fig. 1). We have also described cyclic[18] and acyclic phosphonates[19] and phosphorothioates[20] with potent receptor-selective agonist or antagonist activities. We now describe a synthetic route to two neutral phosphomimetics, in which the *sn*-3 phosphate monoester is replaced by either a trifluoromethanesulfonamide (TfN–) or trifluoromethanesulfonamidoxy (TfNO–) moiety. A related phosphomimetic strategy had been previously exploited to produce a sulfonamide analogue of PC as an inhibitor of synovial PLA_2,[21] as well as a trifluoromethylsulfonamide analogue of phosphotyrosine as an inhibitor of the phosphatase.[22] Based on electronics, size, and H-bonding potential, among other factors, it has been shown that sulfonamide-based 'phosphate isosteres'[23] could act as cell-permeant effectors and inhibitors.[21]

2. Results and discussion

The synthesis of TfN analogues (Scheme 1) commenced with esterification of (*R*)-glycidol (**3**) with saturated (octanoic and palmitic) and unsaturated (oleic) acid using carbodiimide chemistry in good yields. These three acyl chains were selected to provide water-soluble (octanoate) or isoform-targeted analogues (palmitate and oleate). Next, a *trans* stereo- and regio-selective epoxide ring opening was accomplished in a single step to obtain the TfN–LPA analogues.[24] Thus, **4** was reacted neat with trifluoromethylsulfonamide ($TfNH_2$) and a catalytic amount of anhydrous Na_2CO_3 at 90 °C, providing the secondary alcohols **5a**–**c** in up to 85%. Under these conditions, the stereogenic carbon C-2 remains unchanged.[24] The purity of TfN–LPA compounds **5a**–**c** after flash chromatography was verified by ^{19}F NMR to be >99%. Next, esterification of the *sn*-2 hydroxyl group afforded the desired TfN–PA analogues **6a**–**c** in up to 65% yield.

The TfNO–LPA and TfNO–PA analogues were synthesized from enantiomerically pure (*S*)-solketal (**7**, Scheme 2). First, condensation of alcohol **7** with *N*-hydroxyphthalimide under Mitsunobu conditions.[25,26] gave, after purification, intermediate **8** in 94% yield. Phthalimide deprotection with hydrazine monohydrate,[26] followed by amidation with 0.5 M triflic chloride (TfCl), DMAP and pyridine led to compound **10**. Next, acidic cleavage of the isopropylidene group with methanolic *p*-TsOH produced the expected diol **11** in 89% yield. Initial attempts to perform DCC—promoted selective esterification of the primary hydroxyl



Scheme 2.

group[27,28] of diol **11**, at 0–3 °C in CH_2Cl_2, gave disappointing yields. However, selective acylation was readily accomplished in up to 70% yield, using 0.95 equiv of the acyl chloride in anhydrous THF at −78 °C and 2,4,6-collidine as the base.[29] A small amount of diester and 2-acyl isomer were obtained. Based on ^{19}F NMR, the purity of the final compounds was calculated to be 95% for **12a** and 91% for **12b**. By performing the acylation of diol **11** with 2 equiv of acyl chloride at room temperature, the TfNO–PA analogues **13** were obtained in 57% yield.

The method described herein for the synthesis of LPA and PA neutral analogues is facile and flexible with respect to the backbone substituents as well as the choice of acyl chain. Each of the LPA and PA analogues was compared with LPA for potential agonist or antagonist activity toward each of the LPA_{1-4} receptors,[19,20] and as potential inhibitors of LPP.[30] Despite the utility of this phosphate isostere in other lipid and protein phosphate contexts, neither agonist, antagonist, nor inhibitory activity was observed for any of the TfN–LPA, TfN–PA, TfNO–LPA, or TfNO–PA analogues (A. Morris, J. Aoki, personal communication). This appears to support the requirement of an anionic head group for analogues of LPA for proper activation of the LPA GPCRs.[31]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.08.066.

References and notes

1. Feng, L.; Mills, G. B.; Prestwich, G. D. *Expert Opin. Ther. Pat.* **2003**, *13*, 1619–1634.
2. Mills, G. B.; Moolenaar, W. H. *Nat. Rev. Cancer* **2003**, *3*, 582–591.
3. Moolenaar, W. H. *Exp. Cell. Res.* **1999**, *253*, 230–238.
4. Lee, C. W.; Rivera, R.; Gardell, S.; Dubin, A. E.; Chun, J. *J. Biol. Chem.* **2006**, *281*.
5. Kotarsky, K.; Boketoft, A.; Bristulf, J.; Nilsson, N. E.; Norberg, A.; Hansson, S.; Sillard, R.; Owman, C.; Leeb-Lundberg, F. L.; Olde, B. *J. Pharmacol. Exp. Ther.* **2006**, *318*.
6. McIntyre, T. M.; Pontsler, A. V.; Silva, A. R.; St Hilaire, A.; Xu, Y.; Hinshaw, J. C.; Zimmerman, G. A.; Hama, K.; Aoki, J.; Arai, H.; Prestwich, G. D. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 131–136.
7. Zhang, C.; Baker, D. L.; Yasuda, S.; Makarova, N.; Balazs, L.; Johnson, L. R.; Marathe, G. K.; McIntyre, T. M.; Xu, Y.; Prestwich, G. D.; Byun, H. S.; Bittman, R.; Tigyi, G. *J. Exp. Med.* **2004**, *199*, 763–774.
8. Gardell, S. E.; Dubin, A. E.; Chun, J. *Trends Mol. Med.* **2006**, *12*, 65–75.
9. Prestwich, G. D.; Xu, Y.; Qian, L.; Gajewiak, J.; Jiang, G. *Biochem. Soc. Trans.* **2005**, *33*, 1357–1361.
10. Sasagawa, T.; Okita, M.; Murakami, J.; Kato, T.; Watanabe, A. *Lipids* **1999**, *34*, 17–21.
11. Fang, X.; Gaudette, D.; Furui, T.; Mao, M.; Estrella, V.; Eder, A.; Pustilnik, T.; Sasagawa, T.; Lapushin, R.; Yu, S.; Jaffe, R. B.; Wiener, J. R.; Erickson, J. R.; Mills, G. B. *Ann. N. Y. Acad. Sci.* **2000**, *905*, 188–208.
12. Raj, G. V.; Sekula, J. A.; Guo, R.; Madden, J. F.; Daaka, Y. *Prostate* **2004**, *61*, 105–113.
13. Zimmerberg, J. *Traffic 1* **2000**, 366–368.
14. Brindley, D. N.; English, D.; Pilquil, C.; Buri, K.; Ling, Z. C. *Biochim. Biophys. Acta* **2002**, *1582*, 33–44.
15. Jasinska, R.; Zhang, Q. X.; Pilquil, C.; Singh, I.; Xu, J.; Dewald, J.; Dillon, D. A.; Berthiaume, L. G.; Carman, G. M.; Waggoner, D. W.; Brindley, D. N. *Biochem. J.* **1999**, *340*, 677–686.
16. Xu, J.; Love, L. M.; Singh, I.; Zhang, Q. X.; Dewald, J.; Wang, D. A.; Fischer, D. J.; Tigyi, G.; Berthiaume, L. G.; Waggoner, D. W.; Brindley, D. N. *J. Biol. Chem.* **2000**, *275*, 27520–27530.
17. Hooks, S. B.; Santos, W. L.; Im, D. S.; Heise, C. E.; Macdonald, T. L.; Lynch, K. R. *J. Biol. Chem.* **2001**, *276*, 4611–4621.
18. Xu, Y.; Jiang, G.; Tsukahara, R.; Fujiwara, Y.; Tigyi, G.; Prestwich, G. D. *J. Med. Chem.* **2006**, *49*, 5309–5315.
19. Xu, Y.; Aoki, J.; Shimizu, K.; Umezu-Goto, M.; Hama, K.; Takanezawa, Y.; Yu, S.; Mills, G. B.; Arai, H.; Qian, L.; Prestwich, G. D. *J. Med. Chem.* **2005**, *48*, 3319–3327.
20. Qian, L.; Xu, Y.; Simper, T. D.; Jiang, G.; Aoki, J.; Umezo-Goto, M.; Arai, H.; Yu, S.; Mills, G. B.; Tsukahara, R.; Makarova, N.; Fujiwara, Y.; Tigyi, G.; Prestwich, G. D. *Chem. Med. Chem.* **2006**, *1*, 376–383.
21. Pisabarro, M. T.; Ortiz, A. R.; Palomer, A.; Cabre, F.; Garcia, L.; Wade, R. C.; Gago, F.; Mauleon, D.; Carganico, G. *J. Med. Chem.* **1994**, *37*, 337–341.
22. Beaulieu, P. L.; Cameron, D. R.; Ferland, J.-M.; Gauthier, J.; Ghiro, E.; Gillard, J.; Gorys, V.; Poirier, M.; Rancourt, J.; Wernic, D.; Llinas-Brunet, M.; Betageri, R.; Cardozo, M.; Hickey, E. R.; Ingraham, R.; Jakes, S.; Kabcenell, A.; Kirrane, T.; Lukas, S.; Patel, U.; Proudfoot, J.; Sharma, R.; Tong, L.; Moss, N. *J. Med. Chem.* **1999**, *42*, 1757–1766.
23. Rye, C. S.; Baell, J. B. *Curr. Med. Chem.* **2005**, *12*, 3127–3141.
24. Penso, M.; Albanese, D.; Landini, D.; Lupi, V. *Chem. Lett.* **2001**, *5*, 400–401.
25. Mitsunobu, O.; Wada, M.; Sano, T. *J. Am. Chem. Soc.* **1972**, *94*, 679–680.
26. Bailey, S.; Harnden, M. R.; Jarvest, R. L.; Parkin, A.; Boyd, M. R. *J. Med. Chem.* **1991**, *34*, 57–65.
27. Martin, S. F.; Josey, J. A. *Tetrahedron Lett.* **1988**, *29*, 3631–3632.
28. Hebert, N.; Beck, A.; Lennox, R. B.; Just, G. *J. Org. Chem.* **1992**, *57*, 1777–1783.
29. Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 3791–3793.
30. Smyth, S. S.; Sciorra, V. A.; Sigal, Y. J.; Pamuklar, Z.; Wang, Z.; Xu, Y.; Prestwich, G. D.; Morris, A. J. *J. Biol. Chem.* **2003**, *278*, 43214–43223.
31. Fujiwara, Y.; Sardar, V.; Tokumura, A.; Baker, D.; Murakami-Murofushi, K.; Parrill, A.; Tigyi, G. *J. Biol. Chem.* **2005**, *280*, 35038–35050.