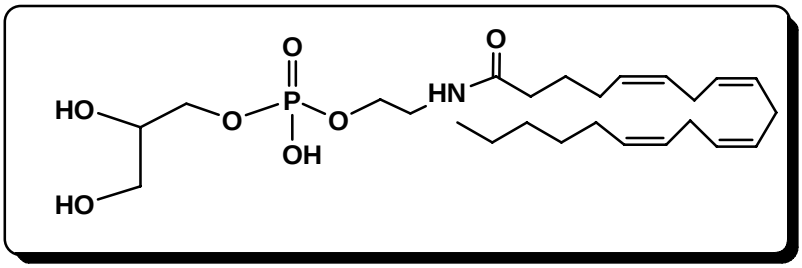
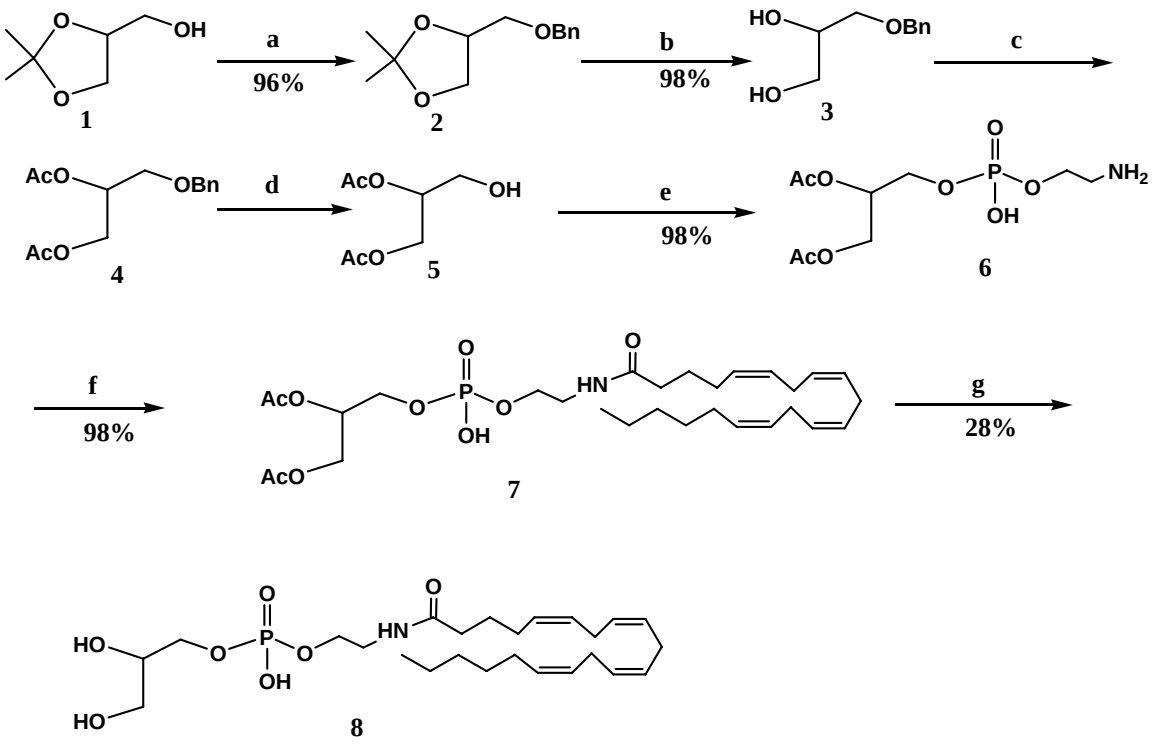


The synthesis of Glycerophosphoanadamide (GPNAE, **8**, Scheme I) was achieved from the commercially available solketal (1) which, is synthetically manipulated to give **5** with a free primary hydroxyl group. The key step in the synthesis involves the conversion of the primary alcohol in **5** to the corresponding phosphatidylethanolamine (**6**) using the established protocol[1] as shown in Scheme 1. It was then coupled to arachidonic acid to give the diacetate 7 which, on hydrolysis of the acetyl protecting group gave the desired GPNAE.

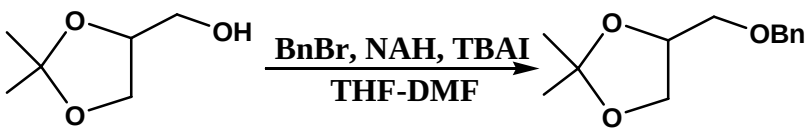
References:

1) (a) Eibl, H. " Phospholipid synthesis: Oxazaphospholanes and dioxaphospholanes as intermediates." *Proc. Natl. Acad. Sci.* **1978**, 75, 9, 4074-4077. (b) Li, R.; Pascal, R. A. " Sulfur-Substituted Phosphatidylethanolamines." *J. Org. Chem.* **1993**, 58, 1952-1954.



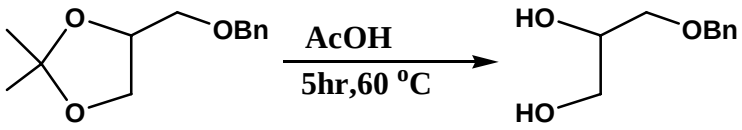
Scheme I. Reagents and conditions: (a) BnBr, NaH, TBAI (b) AcOH, 5 hrs (c) Ac_2O, Et_3N, DMAP, CH_2Cl_2 (d) H_2(g), Pd/C, MeOH(e) 1)$POCl_3$ 2) $NH_2CH_2CH_2OH$ 3) 2-propanol, H_2O, CH_3COOH (f) $NaHCO_3$, arachiodonic ester, THF:H_2O (g) LiOH.H_2O, MeOH:H_2O.

Synthesis of 4-Benzyloxymethyl-2,2-dimethyl-[1,3]dioxolane (2):



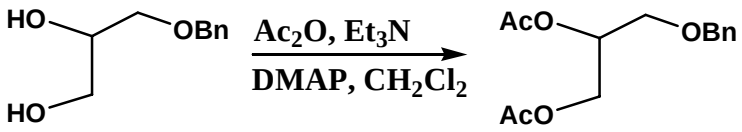
Solketal (1, 5.6 g, 42.9 mmol) was dissolved in anhydrous THF (20 mL) with minimum amount of DMF (2 mL); to this was added catalytic amount of (tetrabutylammoniumiodide, TBAI). To the reaction mixture was then added NaH (5.1 g, 214.5 mmol), this was then cooled to 0^oC. Benzyl bromide was then added drop wise (7.6 mL, 64.4 mmol). After 5 minutes at 0^oC, the cooling bath was removed and this was stirred overnight at room temperature. Next day, the reaction was quenched by adding a few drops of MeOH and concentrated to dryness on rotavap. This was then diluted with EtOAc, washed with water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water/$HCl_{(aq)}$/H_2O/brine, dried under Na_2SO_4 and concentrated; the residue was purified by flash chromatography on silica gel (2% ethyl acetate/hexane). Yield: 9.1 g (96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.0 (brs, 1H), 7.5-7.6 (m, 1H), 7.23-7.59 (m, 1H), 2.28 (s, 3H).

Synthesis of 3-Benzyloxy-propane-1,2-diol (3):



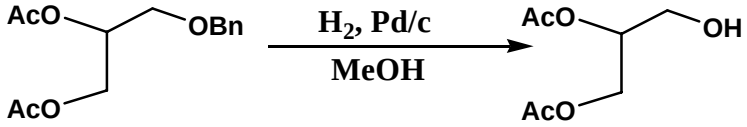
4-Benzyloxymethyl-2,2-dimethyl-[1,3]dioxolane (**2**, 9.1 g) was dissolved in 10% acetic acid (250 mL) and was stirred at 60 ^oC for 5 hrs after which TLC indicated completion of reaction. The reaction mixture was extracted 3 times with EtOAc. The combined organic layers were washed with saturated $NaHCO_3$/brine dried under $Na_2SO_{4(s)}$, filtered and concentrated. This was used directly for the next step. Yield: 7.3 g (98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.28-7.39 (m, 5H), 4.55 (m, 2H), 3.87-3.93 (m, 1H), 3.52-3.74 (m, 5H), 2.1 (s, 1H).

Synthesis of Acetic acid 2-acetoxy-1-benzyloxymethyl-ethyl ester (4):



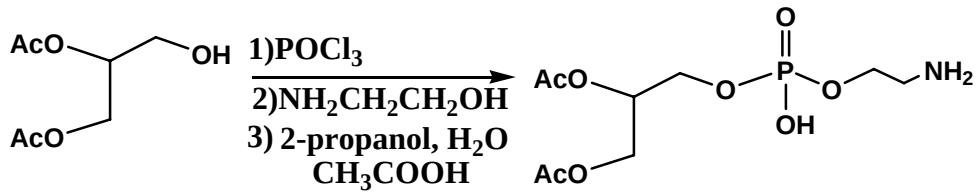
To a suspension of 3-Benzyloxy-propane-1,2-diol (**3**, 7.3 g, 40.1 mmol) in CH_2Cl_2 under N_2 atm was added DMAP (catalytic amount), followed by Et_3N (33 mL, 240.9 mmol), to this was then added drop wise Ac_2O (11.3 mL, 120.4 mmol). After stirring this mixture overnight at rt, it was diluted with CH_2Cl_2 and was washed with H_2O/Brine, dried under $Na_2SO_{4(s)}$. The solvent was evaporated and the residue was subjected to flash column chromatography on silica gel (2% ethyl acetate/hexanes) to get the pure acetyl compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26-7.37 (m 5H), 5.18-5.2 (m 1H), 4.46-4.58 (m, 2H), 4.31-4.36 (m, 1H), 4.12-4.21(m, 1H), 3.59 (d, J = 5.1 Hz, 2H), 2.06 (s, 3H), 2.03 (s, 3H).

Synthesis of Acetic acid 2-acetoxy-1-hydroxymethyl-ethyl ester (5):



2-acetoxy-1-benzyloxymethyl-ethyl ester (**4**) was dissolved in anhydrous MeOH and to it was added 10% $Pd(OH)_2$/C (wet), this was degassed and purged with $N_{2(g)}$. Next it was subjected to hydrogenation via $H_{2(g)}$ dispensed through a balloon, this was stirred overnight at rt. Next day the reaction mixture was filtered through a bed of celite and the residue was washed with EtOAc. This was then concentrated and purified via column chromatography (20% ethyl acetate/hexanes). Yield: 5.0 g (98%, 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.0-5.1 (m, 1H), 4.1-4.3 (m, 3H), 3.75 (d, J = 5.2 Hz, 2H), 2.12 (s, 3H), 2.10 (s, 3H).

Synthesis of Acetic acid 2-acetoxy-1-[(2-amino-ethoxy)-hydoxy-phosphoryloxymethyl]-ethyl ester (6).

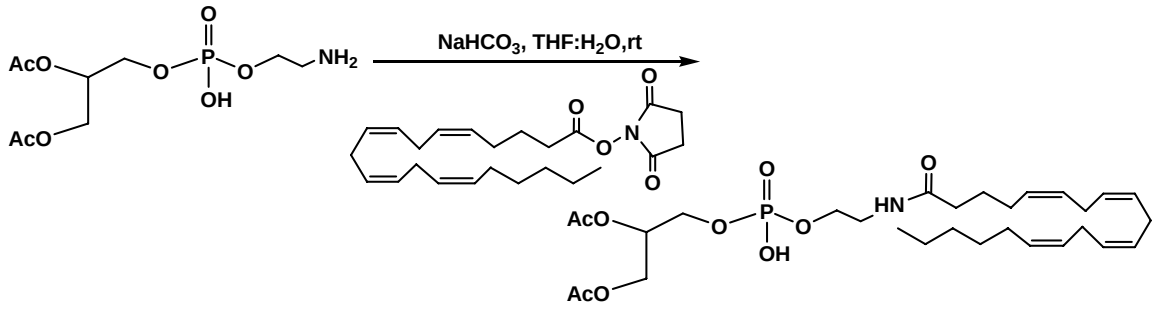


Et_3N (2.2 mL, 16.4 mmol) in trichloroethylene (TCE) was added to a solution of $POCl_3$ (1.53 mL, 16.4 mmol) in hexane at 0 ^oC. After 5 minutes of stirring, 2-acetoxy-1-hydroxymethyl-ethyl ester (**5**) in TCE (15 mL) was added drop wise at 5 ^oC over 5 minutes under a current of $N_{2(g)}$. This was stirred for 30 minutes at 5 ^oC. TLC indicated that all the starting material was converted to dichloride, this was filtered to get rid of the precipitated diethyl ammonium chloride salt. To the filtrate was added some toluene and it was concentrated to give a reddish oily residue.

Next, this residue was dissolved in 25 mL anhydrous THF and was cooled to 10 ^oC. to this was added a mixture of Et_3N (7.1 mL, 51.0 mmol), ethanolamine (0.81 mL, 13.6 mmol) in 25 mL anhydrous THF drop wise via an addition funnel over a period of 5 minutes. This was stirred at 10 ^oC for 10 minutes, after which TLC indicated completion of reaction. This was then quenched by filtering the precipitated triethyl ammonium chloride salt. This was then concentrated and used directly for the next step.

The above oil was dissolved in a mixture of 2-propanol:H_2O:AcOH(10:4:1, 180 mL). This was stirred at rt for 3 hrs after which it was concentrated and used directly for the next step. Yield: 4.12 g (99%). ^1H NMR (300 MHz, MeOH.d_3) δ: 5.48 (d, J = 2.4 Hz, 2H), 5.17-5.22 (m, 1H), 4.0-4.4 (m, 3H), 3.1-3.2(m, 3H), 2.1 (brs, 6H), 2.03-2.07 (m, 3H). (M+1)/Z = 300.1.

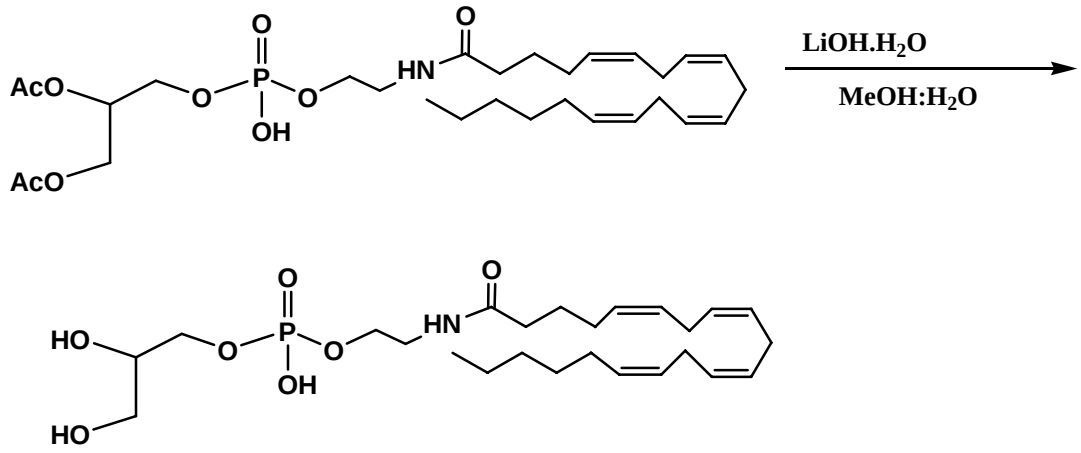
Synthesis of Acetic acid 2-acetoxy-3-[(2-eicosa-5,8,11,14-tetraenoylamino-ethoxy)-hydroxy-phosphoryloxy]-propyl ester (7):



The phosphorylethanolamine (**6**, 2.12 g, 7.0 mmol) was dissolved in H_2O/THF (12:10) solution and to this was added $NaHCO_{3(s)}$, next arachiodonic ester was dissolved in THF was added and stirred at rt overnight.

Next day TLC indicated completion of reaction, the THF was concentrated and the reaction mixture was acidified to pH=2 (checked by pH meter). Next this was diluted with some H_2O and extracted with CH_2Cl_2. This was washed with brine, dried under $Na_2SO_{4(s)}$ and concentrated. Yield: 0.36 g (98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.29-5.39 (m, 8H), 5.19-5.20 (m, 1H), 4.1-4.3 (m, 3H), 3.9-4.0 (m, 3H), 3.67-3.74 (m, 1H), 2.77-2.84 (m, 6H), 2.16-2.2 (m, 2H), 2.03-2.09 (m, 2H), 1.96-2.12 (m, 15H), 1.69-1.72 (m, 2H), 0.87 (t, *J* = 6.8 Hz, *J* = 6.6 Hz, 3H). (M+1)/Z = 586.3.

Synthesis of Phosphoric acid 2,3-dihydroxy-propyl ester 2-eicosa-5,8,11,14-tetraenoylamino-ethyl ester (**8**):



Acetic acid 2-acetoxy-3-[(2-eicosa-5,8,11,14-tetraenoylamino-ethoxy)-hydroxy-

phosphoryloxy]-propyl ester (**7**, 0.36 g, 0.6 mmol) was dissolved in a 5:1 mixture of MeOH: H_2O, to this was added LiOH (0.07 g, 1.8 mmol) and this was stirred overnight at rt. Next day TLC indicated completion of reaction, the MeOH was concentrated on rotovap and the reaction mixture was diluted with CH_2Cl_2, to this was added drop wise 1N HCl until the pH was acidic. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried under $Na_2SO_{4(s)}$. This was then purified (Combiflash) by reverse phase column using water and methanol as the gradient. Yield: 86.6 mg (28.0%). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.28 (t, J = 4.8 Hz, J = 4.8 Hz, 1H). 5.31-5.38 (m, 8H), 3.62-3.67 (m, 3H), 3.43-3.45 (m, 1H), 3.27-3.35 (m, 6H), 3.14-3.17 (m, 2H), 2.76-2.81 (m, 6H), 2.02-2.07 (m, 6H), 1.50-1.58 (m, 2H), 1.26-1.33 (m, 6H), 0.85 (t, J = 6.8 Hz, J = 6.0 Hz, 3H). (M-1)/Z = 500.3.