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TETRAHEDRON

Synthesis of Deoxy Phosphatidylinositol Analogues and Phosphonate Isosters of Ins(1,4,5)P3

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This paper is dedicated to the memory of Dr. S. D. Gero.

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Abstract : The synthesis of phosphatidylinositol analogues, 6-deoxy Ins 1-(1,2-di-*O*-palmitoyl-*sn*-glycero)phosphate and 4,5-bisphosphate derivatives is presented. Two series of phosphonate isosters, 6-deoxy Ins(1)-butylphosphonate and 6-deoxy Ins(1)-*C*-methylenephosphonate as well as its 4,5-bisphosphate analogue were also prepared. All phosphoinositide analogues were obtained from cyclohexanone polyol derived from the D-galactose. Modification of charge distribution at position 1 of PtdIns and InsP derivatives, by replacement of a P-OH group by an alkyl substitution or a P-C bond, resistant to cleavage by lipases, could induce inhibition of activity at further strategic enzymatic levels of the inositide cascade.

Agonist stimulated hydrolysis of phosphatidylinositol-4,5-bisphosphate [PtdIns(4,5)P_2] is the first step in the transmembrane signalling mechanism when cells respond to external stimuli. Under control of activated phospholipase C (PLC) *via* G-protein, two second messengers D-*myo*-inositol-1,4,5-trisphosphate [Ins(1,4,5)P_3] and diacylglycerol (DG) are released into the cell.[1] From Ins(1,4,5)P_3, enzymatic process under phosphatases or kinases control affords subsequent inositol phosphate metabolites with still controversial biological role. During the last decade, the synthesis of modified inositol phosphate derivatives has been strongly investigated[2,3] and phosphatidylinositol analogues are now prone to evaluation.[4] Structural mimics of phosphatidylinositols might be anticipated to interfere with enzyme kinases generating PtdIns phosphate metabolites from PtdIns, or with phospholipases at the early steps of phosphoinositide cascade.[5] Phospholipases are an important class of enzymes for growth factors and oncogene intracellular signalling.[6] Along this line, we envisioned the synthesis of 6-deoxy-D-*myo*-inositol-1-(1,2-di-*O*-palmitoyl-*sn*-glycero)phosphates and 4,5-bisphosphate derivatives. Deoxy analogues of PtdIns have already shown promising antitumoral activity.[7] Complementarily, the synthesis of deoxy-*myo*-inositol phosphonates, has been considered as an interesting tool to interfere with the phosphoinositol transduction pathway, or mimicking the original PtdIns precursors. Two series of phosphonate isosters, 6-deoxy-D-*myo*-inositol-1-(butyl)phosphonate and 6-deoxy-D-*myo*-inositol-1-(*C*-methylene)phosphonate as well as their 4,5-bisphosphate analogues, were then prepared. 6-Deoxy-Ins(1,4,5)P_3 has already been shown to be a full agonist for Ca^{2+} release in

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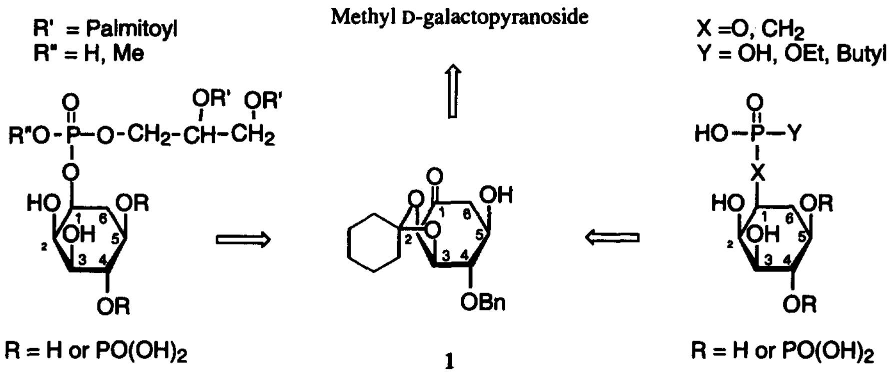
permeabilized SH-SY5Y human neuroblastoma cells, a relatively potent Ins(1,4,5)P_3 5-phosphatase inhibitor and a weak substrate for Ins(1,4,5)P_3 3-kinase.[8] Modifications of Ins(1,4,5)P_3 into lipophilic derivatives have undergone promising property with the aim of incorporating the membrane of intact cells.[3a] Therefore, *C*-1 phosphonate analogues of Ins(1)P and Ins(1,4,5)P_3, associated with the lack of the 6-OH function, might affect the enzymatic dephosphorylation processes releasing inositol phosphate metabolites from Ins(1,4,5)P_3. Specific Ins(1,4,5)P_3 receptor's deactivation by 6-deoxy-Ins(1)-*C*-methylenephosphonate-(4,5)P_2 and consequently influence on the Ca^{2+} mobilization from endoplasmic reticulum could also be expected.

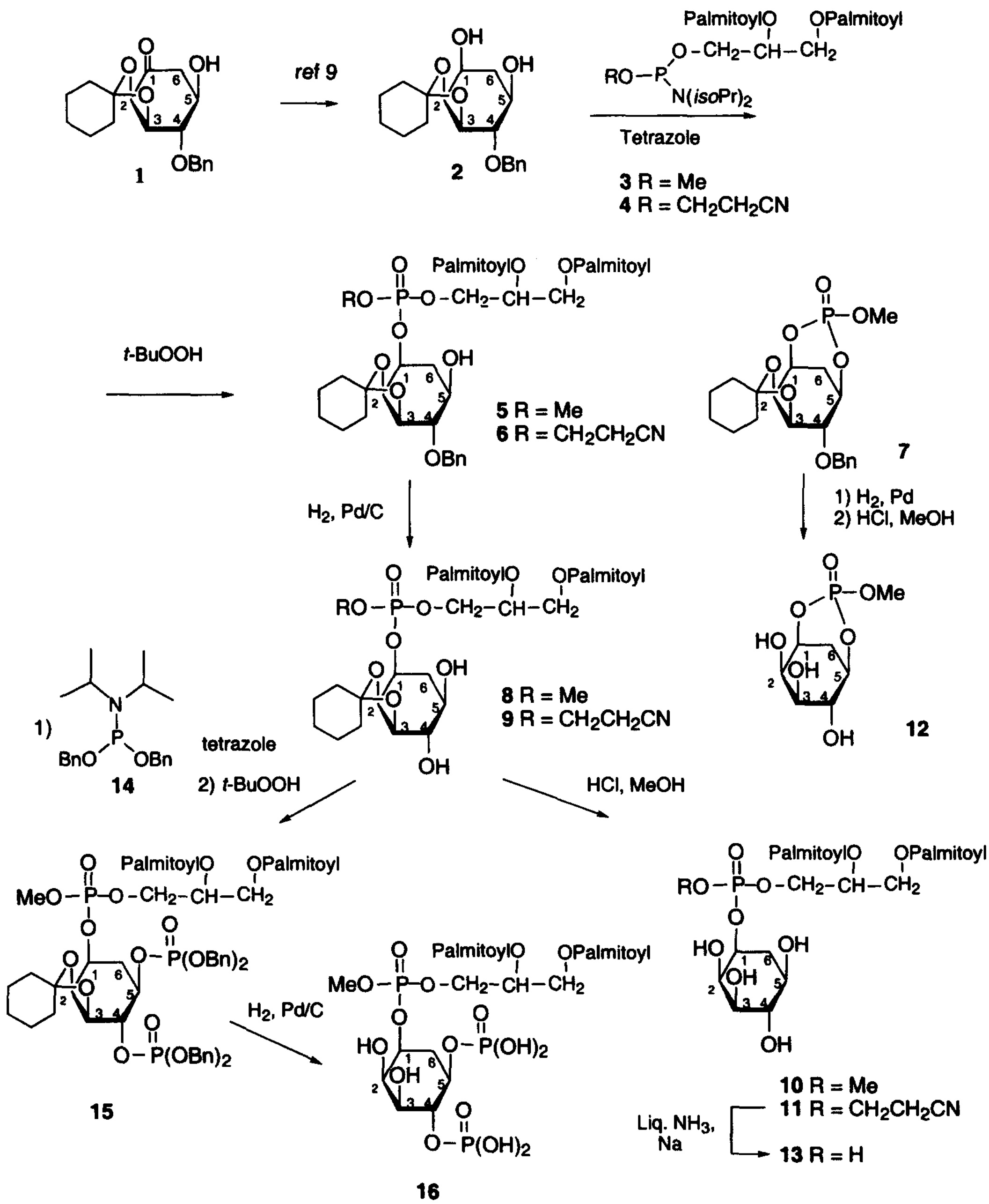
In continuation of our study on the synthesis of deoxy inositol ring from D-galactose, the inosose **1**, resulting from the Ferrier rearrangement of hexenogalactopyranoside precursor,[9] has been regarded as the suitable intermediate to accede to the proposed PtdIns analogues and phosphonate isosters of 6-deoxy InsP.



Retrosynthesis

RESULTS AND DISCUSSION

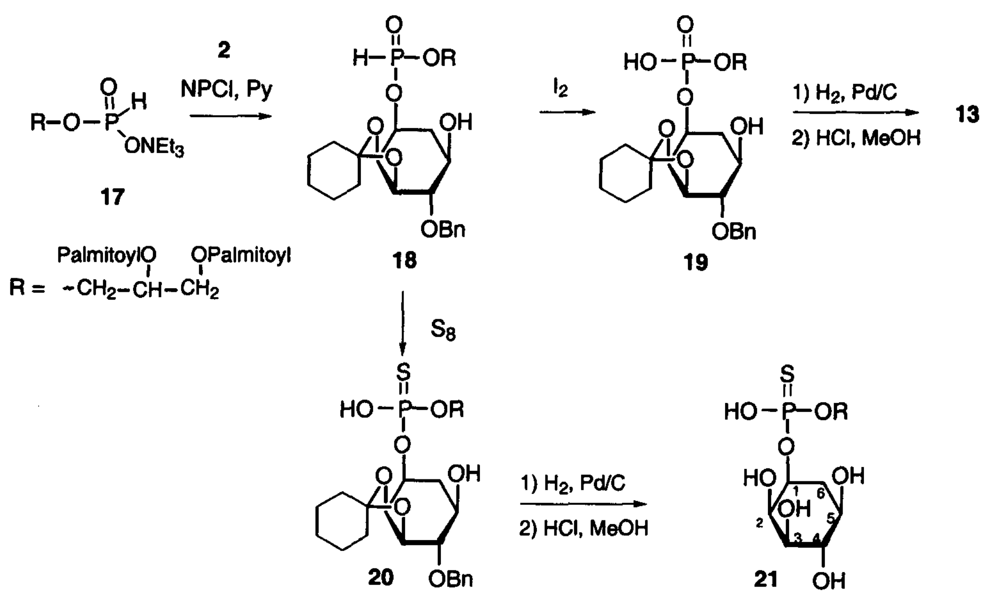
As described recently, the protected 6-deoxy Ins(1,5)diol **2** is easily available by the stereoselective reduction of ketone **1** (**Scheme 1**). Phosphite triester chemistry,[10,7] selected to minimize problems arising from steric hindrance, was applied to compound **2** to produce 6-deoxy PtdIns analogues. Thus, activated phosphites **3** and **4**, bearing a protected 1,2-di-*O*-palmitoyl-*sn*-glycerol, were first prepared from diisopropylaminochloro(methoxy)phosphine and corresponding cyanoethoxy analogue, respectively. Selective reaction of the diol **2** was attempted in CH_2Cl_2 in the presence of tetrazole and the resulting phosphite intermediates were oxidized by *t*-butyl hydroperoxide (*t*-BuOOH) to give the protected phosphatidylinositols **5** and **6**, respectively, in 40% overall yields. Surprisingly, the reaction involving the methoxyphosphite reagent **3** led to the concomitant formation of the Ins(1,5)-cyclic phosphate **7** in moderate 11% yield. The catalytic hydrogenolysis of the intermediates **5** and **6**, using 10% Pd/C in EtOH under hydrogen pressure, furnished quantitatively the 4,5-diols **8** and **9**, respectively. Acidic removal of the cyclohexylidene group from **8** and **9**, with methanolic HCl solution, gave the methyl and cyanoethyl 6-deoxy PtdIns **10** and **11** over 90% yield in both cases. A similar hydrogenolysis-hydrolysis reaction sequence was applied to the cyclic phosphate **7** leading to the 6-deoxy-Ins(1,5)-methylcyclic phosphate **12** in 90% yield. Compound **12** could be regarded as an original Ins1P analogue directed upon inhibition of monophosphatases. Finally, the access to the 6-deoxy-D-*myo*-inositol-1-(1,2-di-*O*-palmitoyl-*sn*-glycero)phosphate **13** was attempted from the phosphodiester intermediate **11**, by deprotection of the cyanoethoxy group using liquid ammonia treatment in the presence of a catalytic amount of sodium, but unsuitable transesterification remained difficult to avoid.



Scheme 1

Alternatively, the phosphatidyl diol **8** was phosphorylated following (4,5)-bisphosphitylation procedure using the (dibenzyloxy)diisopropylaminophosphite reagent **14** and tetrazole. Subsequent *t*-BuOOH oxidation gave the corresponding protected trisphosphate **15** in 60% overall yield. Deprotection of the trisphosphates **15** by hydrogenolysis afforded the desired 6-deoxy-D-*myo*-inositol-1-(1,2-di-*O*-palmitoyl-*sn*-glycero)methylphosphate-4,5-bisphosphate **16** isolated as tetra TRIS salt.

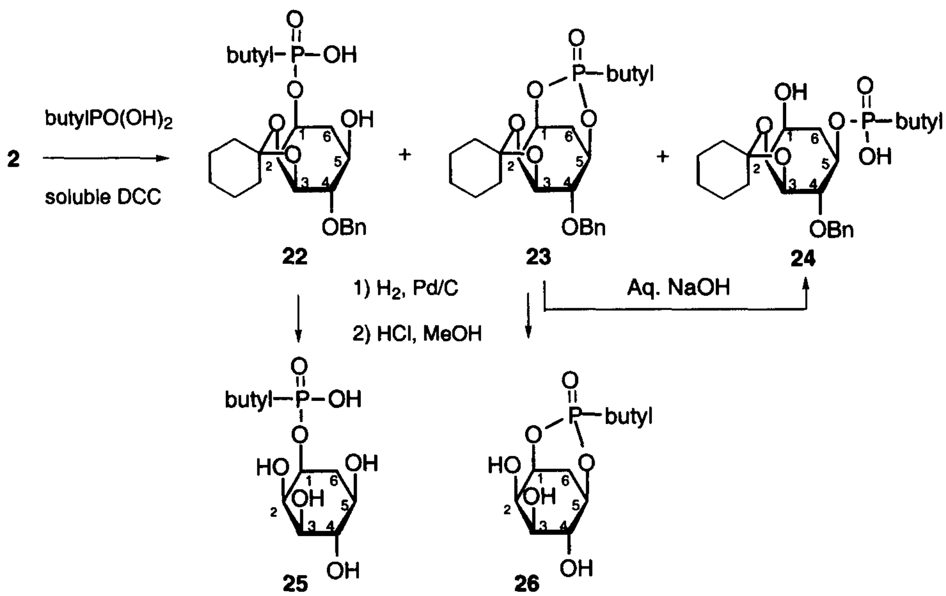
The access to the deoxy phosphatidyl analogue **13** was envisioned more efficiently using the *H*-phosphonate method, developed by Stawinski et al.,[11,4c] involving the (1,2-di-*O*-palmitoyl-*sn*-glycero)-*H*-phosphonate reagent **17** (**Scheme 2**). The glycerophosphonate **17** was first prepared following the described procedure by the reaction of 1,2-dipalmitoyl-*sn*-glycerol in toluene with PCl_3/imidazole complex, in the presence of Et_3N.



Scheme 2

Condensation of **17** with the *myo*-inositol diol **2** was carried out in the presence of 5,5-dimethyl-2-oxo-2-chloro-1,3,2-dioxaphosphorinan (NPCl) in dry pyridine. After neutralization of the medium with triethylammonium bicarbonate and extraction with CH_2Cl_2, the *H*-phosphonate **18** was isolated as a syrup. Subsequent oxidation of intermediate **18**, by addition of iodine in a pyridine/toluene solution, furnished the phosphodiester **19** in 50% overall yield. The use of sulfur (S_8) for the oxidation of compound **18** allowed the access to the corresponding phosphorothioate **20**. Consequently, following a similar hydrogenolysis-hydrolysis sequence as describe previously, the 6-deoxy-D-*myo*-inositol-1-(1,2-di-*O*-palmitoyl-*sn*-glycero)phosphate **13** and its corresponding phosphorothioate **21** (no poisoning of the catalyst was observed) were obtained from their phosphodiester precursors **19** and **20** in 90% overall yields.

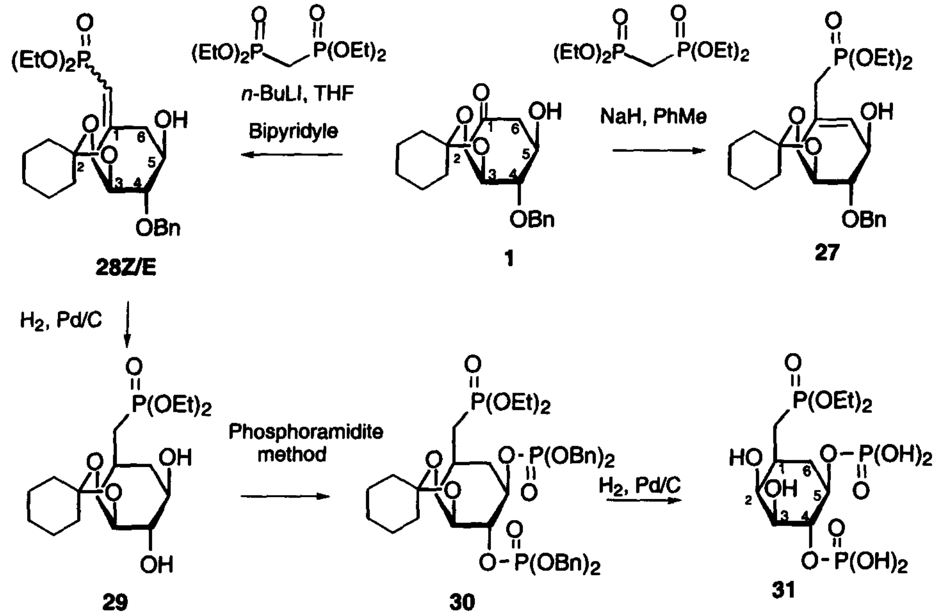
During the course of our research on modified phosphate analogues of inositol metabolites, the synthesis of phosphonate isosters was investigated from the inosose **1** or its corresponding reduced derivative **2**. The condensation of *n*-butyl-phosphonic acid with the 6-deoxy-Ins(1,5)diol **2**, in the presence of trichloroacetonitrile and pyridine, led to the formation of 6-deoxy-Ins(1)-butylphosphonate **22**, (1,5)-butylcyclicphosphonate **23** and (5)-butylphosphonate **24** in 6/1/1 ratio (50% yield) (**Scheme 3**).



Scheme 3

The proportion in the mixture **22/23/24** of the target butylphosphonate **22** was improved to 10/1/2 using *N*-(dimethylaminopropyl)*N'*-ethylcarbodiimide (soluble DCC) as coupling agent in CH_2Cl_2 at reflux. In this latter case, the global yield of the reaction was also increased to 65%. Interestingly, the hydrolysis of the cyclic phosphonate **23**, under basic condition (aq. NaOH), afforded selectively the (5)-phosphonate **24** in quantitative manner. Alternatively, the deprotection of the intermediates **22** and **23** led to the corresponding 6-deoxy Ins(1)-butylphosphonate **25**, isolated as sodium salt in 90% yield, and the (1,5)-butylcyclic phosphonate **26** in 86% yield.

Finally, the synthesis of 1-*C*-(methylene)phosphonate analogues of Ins(1,4,5)P_3 was attempted by a Wittig-Horner reaction from the inosose **1** (**Scheme 4**). The treatment of the cyclohexanone **1** with tetraethyl methylenediphosphonate and *n*-butyllithium, in THF, furnished a mixture of two exovinyl phosphonates **28**, in 70% yield (**28E/Z:** 3.5/1.5). The use of sodium hydride as base, instead of *n*-butyllithium, induced a subsequent migration of the unsaturation into the cycle leading to the cyclohex-1,6-enol **27** in 60% yield. Surprisingly, we were unable to reduce the endocyclic double bond of **27**, whereas, the reduction of the exocyclic vinyl derivatives **28** was achieved under usual hydrogenation conditions (H_2, 10% Pd/C). The reaction applied on the diastereomeric mixture **28 (E/Z)** provided stereoselectively the 1-*C*-methylene diol **29** with subsequent loss of the benzyl ether protection. Thus, phosphorylation of diol **29** was then achieved by phosphoramidite method, using the phosphite reagent **14**, tetrazole and subsequent oxidation with *t*-BuOOH, to give the bis(dibenzyl)phosphate **30** in 70% overall yield from **28**. The hydrogenolysis of the intermediate **30** furnished the 6-deoxy-Ins(1)-*C*-methylenediethylphosphonate-4,5-bisphosphate **31**, isolated as tetra-TRIS salt.



Scheme 4

CONCLUSION

Our contribution in the elaboration of inositol metabolite analogues,[3,9] allowed the synthesis of 6-deoxy PtdIns derivatives and some phosphonate isosters of 6-deoxy-Ins(1)P and 6-deoxy-Ins(1,4,5)P_3. Modification of charge distribution at the position 1 of PtdIns and InsP derivatives, by replacement of a P-OH function by a P-OR group or a P-C bond, resistant to cleavage by lipases, should help to modulate the phosphoinositide cascade turn-over. These analogues are of interest as inhibitors of several enzymatic activation or deactivation processes and appear as new precursors for the synthesis of modified phosphatidylinositol derivatives. As argued in a previous publication,[3a] the transformation of these hydrophilic compounds into lipophilic derivatives, aimed to incorporate the lipidic cell membrane, should be easily envisionned to allow *in vivo* experiments. Therefore, we believe that the synthetic pathway developed from D-galactose, for the stereoselective synthesis of a variety of deoxy *myo*- and *chiro*-inositol precursors of polyphosphate and phosphatidyl derivatives,[3,9] could be extended to the preparation of analogues of inositolphosphoglycan mediators (IPG) or glycosylphosphatidylinositol precursors (GIPs).[12]

Acknowledgements *:* This work was funded by Bayer-AG Geschäftsbereich Pharma und Entwicklung Institut. We thank Dr. E. Bischoff for biological investigations and Professor B. V. L. Potter for fruitful discussions.

EXPERIMENTAL PART

^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker spectrometra WP 200, AC 200, AC 250, WM 400 or ARX 400; chemical shifts are expressed in parts per million (ppm) referenced to TMS or H_3PO_4. Coupling constants (J) are given in hertz (Hz). Multiplicities are recorded as s (singlet), sl (large singulet), d (doublet), t (triplet), q (quartet), and m (multiplet or complex). The $[\alpha]_D$ were recorded on Perkin-Elmer 241-MC sodium absorption at 20°C. Mass spectra (m/z % base peak) were recorded on Atlas CH_4 or AEI MS9 spectrometra. Melting points were determined on a C. REICHERT microscope apparatus and are uncorrected. Elemental analyses were carried out at the "Laboratoire de Microanalyse de l'I.C.S.N." (CNRS, Gif/Yvette). All solvents were freshly distilled prior to use by standard methods[13]. Flash chromatography was performed on silica-gel Merck 60 (230-400 mesh) or licoprep RP-8 resin (15-25µm Merck). Thin layer chromatography was performed on precoated plates of silica gel PF_{254} neutralized with sodium bicarbonate.

4-*O*-Benzyl-2,3-*O*-cyclohexylidene-6-deoxy-D-*myo*-inositol-1-(1,2-di-*O*-palmitoyl-*sn*-glycero)methyl phosphate (5) and 4-*O*-Benzyl-2,3-*O*-cyclohexylidene-6-deoxy-D-*myo*-inositol-1,5-cyclic(methyl)phosphate (7).

A solution of methyl diisopropylaminochlorophosphite **3** (77 mg, 0.39 mmol), Et_3N (0.1 ml) and *sn*-1,2-di-*O*-palmitoyl glycerol (221 mg, 0.39 mmol) in dry CH_2Cl_2 (15 ml) was stirred for 2h at r.t.. Diol **2** (100 mg, 0.3 mmol) and tetrazole (42 mg, 0.6 mmol) were added and the mixture was stirred for a further 6h. The phosphite intermediate obtained was oxidized by addition of *t*-butyl hydroperoxide (*t*-BuOOH, 0.1 ml). The solution was treated by aq. sodium thiosulfate solution and extracted with CH_2Cl_2. The organic layer was evaporated to dryness and the residue was submitted to flash chromatography on silicagel (AcOEt, hexane) to give the phosphatidylinositol **5** (40% yield) and the cyclic phosphate analogue **7** (11% yield) both crystallized from MeOH. Compounds **5** and **7** was isolated under the form of two isomers at the phosphorus atom. Evidence is only provided for this statement by the observation of ^{1}H NMR singlet type signals of the OCH_3 group.

Compound **5**: m.p. 39-41 °C; M.S. (C.I.; isobutanol; m/z): 979 $[MH]^+$, 551 $[CH_2CH(OR)CH_2OR]^+$, 313 $[551\text{-}CH_3(CH_2)_{14}C{=}O + H]^+$, 239 $[CH_3(CH_2)_{14}C{=}O]^+$ with R = $CH_3(CH_2)_{14}C{=}O$; ^{1}H NMR (250 MHz, $CDCl_3$) δ ppm: 5.20 (m, 1H, C*H*CH_2OP), 4.80 (2d, 2H, C*H*$_2$Ph, J_{gem}= 10), 4.65 (m, 1H, H-1), 4.45 (t, 1H, H-2, $J_{2\text{-}1}=J_{2\text{-}3}=3$), 4.41 to 4.0 (m, 5H, H-3, C*H*$_2$OP, C*H*$_2$OCO), 3.76 and 3.84 (2s, 3H, OC*H*$_3$), 3.51 (m, 2H, H-4, H-5), 2.42 to 2.0 (m, 6H, H-6e, H-6a, 2 C*H*$_2$CO), 0.85 (m, 6H, 2C*H*$_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 173.1, 172.2 (C=O), 81.8 (C-4), 78.8 (C-3), 74.7 (C-2), 73.4 (*C*H_2Ph), 71.4 (C-1), 69.3 (C-5, *C*HCH_2OP), 65.6, 61.7 (*C*H_2OP, *C*H_2OC=O), 54.6 (O*C*H_3), 37.4 (C-6); ^{31}P NMR (81 MHz, $CDCl_3$) δ ppm: -0.27; (Found: C, 67.18; H, 10.01; P, 3.68; $C_{55}H_{95}O_{12}P$ requires C, 67.45; H, 9.78; P, 3.16 %). Compound **7**: m.p. 165-167 °C; M.S. (C.I.; isobutanol; m/z): 411 $[MH]^+$; ^{1}H NMR (250 MHz, $CDCl_3$) δ ppm: 4.65 (2d, 2H, C*H*$_2$Ph, J_{gem}= 11), 4.55 (m, 2H, H-1, H-5), 4.35 (t, 1H, H-3, $J_{3\text{-}4}=J_{3\text{-}2}=6$), 4.25 (sl, 1H, H-2), 4.10 (t, 1H, H-4, $J_{4\text{-}3}=J_{4\text{-}5}=6$), 3.30 and 3.20 (2s, 3H, OC*H*$_3$), 2.72 (m, 1H, H-6a, $J_{6a\text{-}6e}=15$), 2.0 (m, 1H, H-6e); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 75.4 (C-4), 73.8, 73.6, 73.3, 73.2 (C-1, C-2, C-3, C-5), 73.3 (*C*H_2Ph), 54.1 (O*C*H_3), 25.3 (C-6); ^{31}P NMR (81 MHz, $CDCl_3$) δ ppm: -9.99; (Found: C, 58.12; H, 6.57; P, 7.52; $C_{20}H_{27}O_7P$ requires C, 58.52; H, 6.62; P, 7.55 %).

4-*O*-Benzyl-2,3-*O*-cyclohexylidene-6-deoxy-D-*myo*-inositol-1-(1,2-di-*O*-palmitoyl-*sn*-glycero)cyanoethyl phosphate (6).

Following the same experimental conditions used for the preparation of compound **5**, using cyanoethyl diisopropylaminochlorophosphite **4** instead of reagent **3**, the phosphatidyl intermediate **6** was isolated in 40% yield from **2**. m.p. 41-43 °C; ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 5.20 (m, 1H, C*H*CH_2OP), 4.75 (m, 2H, CH_2Ph), 4.65 (m, 1H, H-1), 4.50 (sl, 1H, H-2), 4.45 to 3.90 (m, 9H, H-3, CH_2CH_2CN, CH_2OP, $CH_2OC{=}O$), 3.60 (m, 2H, H-4, H-5), 2.80 to 2.0 (m, 10H, H-6a, H-6e, 2 $CH_2CH_2C{=}O$), 0.85 (m, 6H, $2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 173.2, 172.8 (C=O), 116.0 (CN), 82.1 (C-4), 78.9 (C-3), 74.7 (C-2), 73.5 (CH_2Ph) 72.0, (C-1), 69.4, 69.3 (C-5, *C*HCH_2OP), 66.1, 62.2, 61.7 (CHCH_2OP, $CH_2OC{=}O$, CH_2CH_2CN), 37.5 (C-6), 19.5 (CH_2CN), 14.1 (CH_3); ^{31}P NMR (81 MHz, $CDCl_3$) δ ppm: -2.0; (Found: C, 66.85; H, 9.56; N,1.65; P, 3.13; $C_{57}H_{96}O_{12}NP$ requires C, 67.23; H, 9.50; N, 1.38; P, 3.04 %).

2,3-*O*-Cyclohexylidene-6-deoxy-D-*myo*-inositol-1-(1,2-di-*O*-palmitoyl-*sn*-glycero)methyl phosphate (8).

The phosphate **5** (98 mg, 0.1 mmol) dissolved in EtOH (5 ml) was hydrogenated for 4h. at r.t. in the presence of palladium on carbon 10% (Pd/C) at 75 psi. The catalyst was removed by filtration and the diol **8** was isolated after evaporation of the organic solvents under reduced pressure and crystallization from MeOH (quantitative yield). m.p. 46-47 °C; ^1H NMR (250 MHz, $CDCl_3$) δ ppm: 5.25 (m, 1H, C*H*CH_2OP), 4.65 (m, 1H, H-1), 4.40 (sl, 1H, H-2), 4.35 to 4.05 (m, 6H, H-3, H-5, CH_2OP, $CH_2OC{=}O$), 4.0 (t, 1H, H-4, $J_{4\text{-}3}=J_{4\text{-}5}=9$), 3.70 (sl, 3H, OCH_3), 2.50 to 2.0 (m, 6H, H-6a, H-6e, 2 $CH_2C{=}O$), 0.85 (m, 6H, $2CH_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm: 173.3, 173.1 (C=O), 111.6 (O-C-O), 78.7 (C-4), 75.9 (C-3), 74.5 (C-2), 71.6 (C-1), 69.5 (C-5,*C*HCH_2OP), 54.8 (OCH_3), 37.8 (C-6), 14.2 (CH_3); ^{31}P NMR (81 MHz, $CDCl_3$) δ ppm: -0.73; (Found: C, 65.27; H, 10.10; P, 3.87; $C_{48}H_{89}O_{12}P$ requires C, 64.83; H, 10.09; P, 3.48 %).

2,3-*O*-Cyclohexylidene-6-deoxy-D-*myo*-inositol-1-(1,2-di-*O*-palmitoyl-*sn*-glycero) cyanoethyl phosphate (9).

Following the same experimental conditions used for the preparation of compound **8**, the phosphatidylinositol **9** was isolated in quantitative yield from **6**. m.p. 41-43 °C; ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 5.22 (m, 1H, C*H*CH_2OP); 4.60 (m, 1H, H-1); 4.47 (sl, 1H, H-2); 4.45 to 3.85 (m, 9H, H-3, CH_2CH_2CN; CH_2OP et $CH_2OC{=}O$); 3.62 (m, 2H, H-4, H-5); 2.81 to 2.10 (m, 10H, H-6e, H-6a, $2CH_2CH_2C{=}O$); 0. 82 (m, 6H, $2CH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 173.0, 172.5 (2*C*=O); 115.4 (*C*N); 82.2 (C-4); 79.1 (C-3); 74.6 (C-2); 71.8 (C-1); 69.5, 69.1 (C-5, *C*HCH_2OP); 66.0, 62.4, 61.9 (CHCH_2OP; $CH_2OC{=}O$; CH_2CH_2CN); 36.9 (C-6); 19.5 (CH_2C N); 14.3 (CH_3).

6-Deoxy-D-*myo*-inositol-1-(1,2-di-*O*-palmitoyl-*sn*-glycero)methyl phosphate (10).

The ketal **8** (90 mg, 0.1 mmol), dissolved in methanol (10ml)-conc. HCl (2ml) solution, was stirred for 3h. at r.t.. After neutralization of the solution by sodium bicarbonate, filtration on Celite with AcOEt and partial concentration of the filtrate, the tetrol **10** was crystallized from MeOH (90% yield). m.p. 70-73 °C; ^1H NMR (250 MHz, $CDCl_3$) δ ppm: 5.25 (m, 1H, C*H*CH_2OP), 4.50 to 4.0 (m, 7H, H-1, H-2, H-3, CH_2OP, $CH_2OC{=}O$), 3.80 (m, 5H, H-4, H-5, OCH_3), 2.35 (m, 6H, H-6a, H-6e, 2 $CH_2C{=}O$), 0.90 (m, 6H, $2CH_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm: 173.6, 173.3 (C=O), 73.0, 72.3, 71.2, 69.6, 68.5 (C-1, C-2, C-3, C-4, C-5, *C*HCH_2OP), 65.2, 61.6 (CH_2OP, $CH_2OC{=}O$), 55.0 (OCH_3), 34.3 (C-6), 14.2 (CH_3); ^{31}P NMR

(81 MHz, C_5D_5N) δ ppm: +0.9; (Found: C, 61.76; H, 10.12; $C_{42}H_{81}O_{12}P.1/2H_2O$ requires C, 61.66; H, 10.10%

6-Deoxy-D-*myo*-inositol-1-(1,2-di-*O*-palmitoyl-*sn*-glycero)cyanoethyl phosphate (11) and 6-Deoxy-D-*myo*-inositol-1-(1,2-di-*O*-palmitoyl-*sn*-glycero) phosphate (13).

Following the same experimental conditions used for the preparation of compound **10**, the phosphatidyl tetrol **11** was obtained in quantitative yield from precursor **9**. The tetrol **11** (crude product) was dissolved in saturated liquid ammonia condensed at -60°C in a solution of methanol. A little amount of sodium metal was then added and the reaction was followed by TLC. After concentration to dryness the phosphoinositide analogue **13** was obtained as sodium salt (70% yield). Compound **13** was also prepared by deprotection of **19** by the same procedure used to prepare compound **21** from **20**, in 88% yield. Compound **13**: ^1H NMR (250 MHz, $CDCl_3$) δ ppm: 5.20 (m, 1H, C*H*CH_2OP), 4.30 (m, 1H, H-1), 4.31-4.0 (m, 6H, H-2, H-3, C*H*$_2$OP, C*H*$_2$OC=O), 3.60 (m, 2H, H-4, H-5), 2.40-2.0 (m, 6H, H-6a, H-6e, 2 C*H*$_2$C=O), 0.90 (m, 6H, 2C*H*$_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm: 173.4 (C=O), 78.9 (C-4), 72.1 (C-2, C-3), 69.3, 68.2 (C-1, *C*HCH_2OP), 65.0 (C-5), 62.5 (*C*H_2OP, *C*H_2OC=O), 34.0 (C-6), 14.1 (*C*H_3); ^{31}P NMR (81 MHz, $CDCl_3$) δ ppm: -1.47; (Found: C, 60.16; H, 9.92; P, 3.53; $C_{41}H_{79}O_{12}P.1H_2O$ requires C, 60.56; H, 9.79; P3.81 %).

6-Deoxy-D-*myo*-inositol-1,5-cyclic (methyl)phosphate (12).

To a solution of cyclic phosphate derivative **7** (80mg, 0.2mmol) in EtOH (10 ml) was added 10% Pd/C (150 mg) and the mixture was stirred for 2h under hydrogen pressure (75 psi). After filtration of the solid on Celite (EtOH) and concentration to dryness of the filtrat, the residue was dissolved in MeOH (10ml) and conc. HCl (1 ml) was then introduced. The solution was stirred for further 3h at r.t. and the organic layer was concentrated. The residue was chromatographed on RP8 (MeOH/H_2O) to give the triol **12** (90% yield). ^1H NMR (250 MHz, $CDCl_3$) δ ppm: 4.65 (m, 1H, H-4), 4.50 (sl, 1H, H-3), 4.20 (sl, 1H, H-2), 4.05 (sl, 1H, H-5), 3.78 to 3.72 (m, 4H, H-1, OC*H*$_3$), 2.70 (m, 1H, H-6a), 2.25 (m, 1H, H-6e); ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm: 80.9 (C-4), 78.0 (C-3), 73.5 (C-2), 71.4 (C-5), 69.2 (C-1), 54.2 (O*C*H_3), 25.5 (C-6); ^{31}P NMR (81 MHz, CD_3OD) δ ppm: -6.46; (Found: C, 33.49; H, 5.68; $C_7H_{13}O_7P.1/2H_2O$ requires C, 33.74; H, 5.66 %).

2,3-*O*-Cyclohexylidene-6-deoxy-D-*myo*-inositol-1-(1,2-di-*O*-palmitoyl-*sn*-glycero)methyl phosphate-4,5-bis(dibenzyl) phosphate (15).

Treatment of diol **8** by phosphoramidite method, using the (dibenzyl)diisopropylaminophosphite reagent **14**, tetrazole and oxidation by *t*-BuOOH, gave the (dibenzyl)phosphate inositol **15** which crystallized from MeOH (60% yield). m.p. 40-42 °C; ^1H NMR (250 MHz, $CDCl_3$) δ ppm: 5.25 (m, 1H, C*H*CH_2OP), 5.12 (m, 8H, C*H*$_2$Ph), 4.61 (m, 2H, H-1, H-4), 4.50 (t, 1H, H-2, $J_{2-1}=J_{2-3}=5$), 4.43 to 4.0 (m, 6H, H-3, H-5, C*H*$_2$OP, C*H*$_2$OC=O), 3.81 (sl, 3H, OC*H*$_3$), 2.49 (m, 1H, H-6e), 2.32 (m, 5H, H-6a, 2 C*H*$_2$C=O), 0.85 (m, 6H, 2C*H*$_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm: 173.3, 172.8 (C=O), 112.1 (OCO), 81.3 (C-4), 74.7 (C-3), 73.5 (C-2), 71.1 (C-1), 69.5 (C-5, *C*HCH_2OP, *C*H_2Ph), 65.9, 61.8 (*C*H_2OP, *C*H_2OC=O), 54.9 (O*C*H_3), 37.5 (C-6), 14.2 (*C*H_3); ^{31}P NMR (81 MHz, $CDCl_3$) δ ppm: -0.95; -0.45; (Found: C, 64.02; H, 8.42; P, 6.63; $C_{76}H_{115}O_{18}P_3.1/2H_2O$ requires C, 63.94; H, 8.26; P, 6.51 %).

6-Deoxy-D-*myo*-inositol-1-(1,2-di-*O*-palmitoyl-*sn*-glycero)methylphosphate-4,5-bis phosphate (16).

The phosphate **15** (70 mg, 0.05 mmol) dissolved in EtOH (5 ml) was hydrogenated for 2h. at r.t. in the presence of 10% Pd/C (100mg) at 75 psi. The catalyst was removed by filtration on Whatman paper (H_2O) and the trisphosphate analogue **16** was isolated by lyophilization, after concentration of the solvents and addition of TRIS salt (24 mg). ^{1}H NMR (250 MHz, D_2O) δ ppm: 5.19 (m, 1H, C*H*CH_2OP), 4.21-3.34 (m, 48H, H-1, H-2, H-3, H-4, H-5, C*H*$_2$OP, C*H*$_2$OC=O, C*H*$_2$OH, OC*H*$_3$), 2.22 (m, 6H, H-6e, H-6a, 2 C*H*$_2$C=O), 1.49 (m, 4H, 2C*H*$_2$$CH_2$C=O), 1.18 (m, 48H, 2C*H*$_2$, 12C*H*$_3$), 0.82 (m, 6H, 2C*H*$_3$); ^{13}C NMR (50 MHz, CD_3OD) δ ppm: 81.3 (C-4), 74.2, 73.7, 72.6 (C-1, C-2, C-3), 70.6 (C-5, CHCH_2OP), 67.2, 62.8 (*C*H_2OP, *C*H_2OC=O), 62.5 (*C*H_2OH), 54.9 (O*C*H_3), 35.0 (C-6), 14.4 (*C*H_3).

4-*O*-Benzyl-2,3-*O*-cyclohexylidene-6-deoxy-D-*myo*-inositol-1-(1,2-di-*O*-palmitoyl-*sn*-glycero)*H*-phosphonate (18); 4-*O*-Benzyl-2,3-*O*-cyclohexylidene-6-deoxy-D-*myo*-inositol-1-(1,2-di-*O*-palmitoyl-*sn*-glycero) phosphate (19) and 4-*O*-Benzyl-2,3-*O*-cyclohexylidene-6-deoxy-D-*myo*-inositol-1-(1,2-di-*O*-palmitoyl-*sn*-glycero) phosphorotioate (20).

The diol **2** (200 mg, 1.8 mmol) and 5,5-dimethyl-2-oxo-2-chloro-1,3,2-dioxaphosphorinane (NPCl, 330 mg, 1.8 mmol) was added to a solution of triethylammonium (1,2-di-O-palmitoyl-*sn*-glycero)*H*-phosphonate compound **17** (480 mg, 0.66 mmol) in pyridine (5 ml). The mixture was stirred for 1h. at r.t. before neutralization with aq. triethylammonium bicarbonate solution (TEAB, 0.1M). Extraction with CH_2Cl_2 and evaporation of the organic layer gave the *H*-phosphonate intermediate **18** which was used without further purification. For the preparation of compound **19**, the *H*-phosphonate intermediate **18** was dissolved in aqueous-pyridine solution (10 ml; 98/2, v/v) and iodide (335 mg, 1.32 mmol) was added. The mixture was stirred for 30 mn. at r.t. before addition of an aqueous solution containing 5% of sodium bisulfite (20 ml). After extraction with CH_2Cl_2 and evaporation of the organic layer, the residue was purified by chromatography on silicagel (AcOEt, CH_3OH) to give the phosphatidyl inositol **19** as solid (50% yield). m.p. 170-172 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ ppm: 5.17 (m, 1H, C*H*CH_2OP), 4.81 (2d, 2H, C*H*$_2$Ph, J*gem*= 10), 4.53 (m, 1H, H-1), 4.35 (sl, 1H, H-2), 4.02 (m, 5H, H-3, C*H*$_2$OP, C*H*$_2$OCO), 3.55 (m, 1H, H-5), 3.46 (t, 1H, H-4, J_{4-3}=J_{4-5}=9Hz), 2.24 (m, 5H, H-6e, 2 C*H*$_2$CO), 1.90 (m, 1H, H-6a), 0.85 (m, 6H, 2C*H*$_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm: 173.9, 173.6 (C=O), 110.7 (OCO), 85.1 (C-4), 79.7 (C-3), 76.0 (C-2), 73.6 (*C*H_2Ph), 70.7 (C-1), 70.1 (*C*HCH_2OP), 68.2 (C-5), 64.1, 63.1 (CH_2OP, *C*H_2OC=O), 34.4 (C-6), 14.2 (CH_3); ^{31}P NMR (81 MHz, $CDCl_3$) δ ppm: -4.11; (Found: C, 64.90; H, 9.76; P, 3.28; $C_{54}H_{93}O_{12}P.2H_2O$ requires C, 64.77; H, 9.76; P, 3.10 %). For the preparation of compound **20:** the *H*-phosphonate intermediate **18** was then dissolved in pyridine-toluene solution (10 ml; 1/1, v/v) and sulfur (48 mg, 1.5 mmol) was added. The mixture was stirred for 8h. at r.t. After extraction with CH_2Cl_2 and evaporation of the organic layer, the residue was purified by chromatography on silicagel (AcOEt, CH_3OH) to give the phosphorothioate analogue **20** (47% yield). ^{1}H NMR(250 MHz, $CDCl_3$) δ ppm: 5.25 (m, 1H, C*H*CH_2OP), 4.78 (2d, 2H, C*H*$_2$Ph, J*gem*= 10), 4.46 (sl, 1H, H-2), 4.42 (m, 1H, H-1), 4.11 (m, 5H, H-3, C*H*$_2$OP, C*H*$_2$OCO), 3.50 (m, 4H, H-4, H-5, 2O*H*), 2.33 (m, 4H, C*H*$_2$C=O), 2.21 to 1.91 (m, 2H, H-6a, H-6e), 0.89 (m, 6H, 2C*H*$_3$); ^{13}C NMR (63 MHz, $CDCl_3$, D_2O) δ ppm: 173.9 (2C=O), 110.9 (OCO), 84.8 (C-4), 79.5 (C-3), 76.0 (C-2), 73.3 (*C*H_2Ph), 70.8 (C-1), 70.5 (*C*HCH_2OP), 68.1 (C-5), 64.4, 62.9 (*C*H_2OP, *C*H_2OC=O), 37.7 (C6), 14.2 (CH_3); (Found: C, 65.89; H, 9.85; P, 2.81; S, 2.96; $C_{54}H_{93}O_{11}PS$ requires C, 66.09; H, 9.55; P, 3.16; S, 3.27 %).

6-Deoxy-D-*myo*-inositol-1-(1,2-di-*O*-palmitoyl-*sn*-glycero) phosphorotioate (21).

To a solution of phosphorothioate intermediate **20** (98 mg, 0.1mmol) in EtOH (10 ml) was added 10% Pd/C (100 mg) and the mixture was stirred for 2h. under hydrogen pressure (75 psi). After filtration of the solid on Celite (EtOH) and evaporation to dryness, the residue was dissolved in MeOH (10ml) and conc. HCl (1 ml) was then introduced. The solution was stirred for further 3h at r.t., neutralized with $NaHCO_3$ and concentrated to dryness. The residue was chromatographed on RP-8 ($MeOH/H_2O$) to give the tetrol **21** (90% yield) isolated as sodium salt. ^1H NMR (250 MHz, $CDCl_3$) δ ppm: 5.20 (m, 1H, $CHCH_2OP$), 4.52 to 4.10 (m, 7H, H-2, H-3, CH_2OP, CH_2OC=O), 3.62 (m, 2H, H-4, H-5), 2.38 to 2.05 (m, 6H, H-6a, H-6e, $2CH_2C$=O), 0.91 (m, 6H, $2CH_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ ppm: 173.9, 173.5 (C=O), 77.8 (C-4), 72.3 (C-2, C-3), 68.4 (C-1, $CHCH_2OP$), 65.1 (C-5), 62.9 (CH_2OP, CH_2OC=O), 34.2 (C-6), 14.1 (CH_3); ^{31}P NMR (81 MHz, $CDCl_3$) δ ppm: +56; (Found: C, 61.10; H, 9.60; P, 3.96; S, 3.58; $C_{41}H_{79}O_{11}PS$ requires C, 60.71; H, 9.81; P, 3.82; S, 3.95 %).

4-*O*-Benzyl-2,3-*O*-cyclohexylidene-6-deoxy-D-*myo*-inositol-1-(*n*-butyl) phosphonate (22) ; 4-*O*-Benzyl-2,3-*O*-cyclohexylidene-6-deoxy-D-*myo*-inositol-1,5-cyclic(*n*-butyl) phosphonate (23) and 4-*O*-Benzyl-2,3-*O*-cyclohexylidene-6-deoxy-D-*myo*-inositol-5-(*n*-butyl) phosphonate (24).

To a solution of diol **2** (300 mg, 0.9 mmol) dissolved in dry CH_2Cl_2 (20 ml) under argon, was added *n*-butylphosphonic acid (400 mg, 1.08 mmol), DCC (860 mg, 4.5 mmol) and dimethylaminopyridine (20 mg, 0.16 mmol). The mixture was stirred for 72h. at reflux, and extracted with CH_2Cl_2. After concentration to dryness of the solution, the residue was chromatographed on silicagel (AcOEt/Heptane then AcOEt/CH_3OH). The cyclic phosphonate derivative **23** was first eluded (AcOEt/Heptane) and isolated as solid (6% yield). Then the mixture of phosphonate compounds **22** and **24** was recovered using (AcOEt/CH_3OH) as eluent. The solution was evaporated and the residue was purified by preparative thin-layer chromatography on RP8 (CH_3OH/H_2O). The 1-phosphonate analogue **22** and its 5-isomer **24** was isolated (38% and 6% yield respectively). Compound **22**: ^1H NMR (250 MHz, CD_3OD) δ ppm: 4.78 (2d, 2H, CH_2Ph, *Jgem*= 11), 4.54 (m, 1H, H-1), 4.42 (sl, 1H, H-2), 4.10 (t, 1H, H-3, $J_{3-2}=J_{3-4}=6$), 3.56 (m, 1H, H-5), 3.44 (dd, 1H, H-4, $J_{4-5}=10$, $J_{4-3}=6$), 2.10 (m, 1H, H-6e), 2.02 (q, 1H, H-6a, $J_{6a-6e}=J_{6a-1}=J_{6a-5}=12$), 0.90 (t, 3H, CH_3, J =6.5); ^{13}C NMR (63 MHz, CD_3OD) δ ppm: 111.5 (OCO), 86.6 (C-4), 81.0 (C-3), 77.8 (C-2), 74.5 (CH_2Ph), 69.8 (C-5), 69.4 (C-1), 35.7 (C-6), 14.2 (CH_3); ^{31}P NMR (81 MHz, $CDCl_3$) δ ppm: +28.33; (Found: C, 56.11; H, 8.20; P, 6.06; $C_{23}H_{35}O_7P.2H_2O$ requires C, 56.31; H, 8.01; P, 6.31 %). Compound **23**: m.p. 135-138 °C; ^1H NMR (250 MHz, $CDCl_3$) δ ppm: 4.70 (s, 2H, CH_2Ph), 4.55 (m, 2H, H-1, H-5), 4.28 (m, 1H, H-3), 4.11 (sl, 2H, H-2, H-4), 3.18 (m, 1H, H-6e), 1.91 (m, 1H, H-6a), 0.88 (t, 3H, CH_3, J =6.5); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 110.2 (OCO), 76.5 (C-4), 74.7, 73.8, 73.1 (C-2, C-3, C-5), 70.5 (CH_2Ph), 68.1 (C-1), 34.4 (C-6), 13.6 (CH_3); ^{31}P NMR(81 MHz, $CDCl_3$) δ ppm: +27.85; (Found: C, 63.46; H, 7.55; P, 6.84; $C_{20}H_{27}O_7P$ requires C, 63.28; H, 7.62; P, 7.10 %). Compound **24**: ^1H NMR (250 MHz, CD_3OD) δ ppm: 4.76 (dd, 2H, CH_2Ph, *Jgem*= 11), 4.28(sl, 1H, H-2), 4.07 (t, 1H, H-3, $J_{3-2}=J_{3-4}=6$), 3.95 (m, 2H, H-1, H-5), 3.51 (dd, 1H, H-4, $J_{4-3}=7$, $J_{4-5}=10$), 2.25 (m, 1H, H-6e, $J_{6e-6a}=12$), 2.04 (m, 3H, H-6a, CH_2P), 0.81 (t, 3H, CH_3, J =6.5); ^{13}C NMR (63 MHz, CD_3OD) δ ppm: 111.3 (OCO), 85.3 (C-4), 80.8 (C-3), 78.2 (C-2), 74.9 (CH_2Ph), 73.2 (C-5), 66.5 (C-1), 36.4 (C-6), 14.1 (CH_3); ^{31}P NMR (81 MHz, CD_3OD) δ ppm: +29.70.

6-Deoxy-D-*myo*-inositol-1-(*n*-butyl) phosphonate (25).

To a solution of compound **22** (46 mg, 0.1mmol) in EtOH (10 ml) was added 10% Pd/C (100 mg) and the mixture was stirred for 2h under hydrogen pressure (75psi). After filtration of the solid on celite (EtOH) and evaporation to dryness, the residue was dissolved in MeOH (10ml) and conc. HCl (1 ml) was then introduced. The solution was stirred for further 3h at r.t., neutralized with $NaHCO_3$ and concentrated to dryness. The residue was chromatographed on RP8 ($MeOH/H_2O$) to give the tetrol **25** (90% yield) isolated as sodium salt. M.S. (C.I.; isobutanol; m/z): 307 $[MH]^+$, ^1H NMR (250 MHz, D_2O) δ ppm: 4.0 (m, 2H, H-2, H-5), 3.78 (m, 1H, H-1, J_{1-6a}=12), 3.60 (t, 1H, H-4, J_{4-3}=J_{4-5}=10), 3.44 (dd, 1H, H-3, J_{3-2}=3, J_{3-4}=10), 2.13 (m, 1H, H-6e, J_{6e-6a}=12), 1.88 (q, 1H, H-6a, J_{6a-1}=J_{6a-5}=J_{6e-6a}=12), 0.86 (t, 3H, CH_3, J =6.5); ^{13}C NMR (50 MHz, C_5D_5N) δ ppm: 73.6 (C-2, C-4, C-5), 73.2 (C-3), 67.3 (C-1), 35.4 (C-6), 13.4 (CH_3); ^{31}P NMR (81 MHz, D_2O) δ ppm: +28.58; (Found: C, 35.66; H, 6.58; P, 8.90; $C_{10}H_{20}O_7PNa.3/2H_2O$ requires C, 36.03; H, 6.95; P, 9.30 %).

6-Deoxy-D-*myo*-inositol-1,5-cyclic (*n*-butyl)phosphonate (26).

Using the same experimental procedure used for the preparation of **25**, the 1,5-cyclic phosphonate **26** was isolated as solid from **23** (86% yield). m.p. 128-132 °C; ^1H NMR (400 MHz, CD_3OD) δ ppm: 4.56 (sl, 1H, H-4), 4.41 (sl, 1H, H-3), 4.15 (sl, 1H, H-2), 4.01 (sl, 1H, H-5), 3.73 (sl, 1H, H-1), 2.90 (m, 1H, H-6e), 2.28 (m, 1H, H-6a), 0.92 (t, 3H, CH_3, J =6.5); ^{13}C NMR (63 MHz, CD_3OD) δ ppm: 77.4 (C-4), 74.6 (C-3), 73.1 (C-2), 72.1 (C-5), 69.2 (C-1), 34.1 (C-6), 13.8 (CH_3); ^{31}P NMR (81 MHz, CD_3OD) δ ppm: +35.44; (Found: C, 43.96; H, 7.41; $C_{10}H_{19}O_6P.1/2H_2O$ requires C, 43.64; H, 7.33 %).

2-D-(2,3,5/4)-4-*O*-Benzyl-2,3-*O*-cyclohexylidene-2,3,4,5-cyclohex-1,6-enetetrol-1-C-methylene(diethyl) phosphonate (27).

To a solution of tetraethyl methylene diphosphonate (1.73 ml, 11.6 mmol) dissolved in dry THF (20 ml) was added NaH (334 mg, 13.92 mmol). The solution was stirred 15 mn. at r.t. before addition of the cyclohexanone **1** (1.9 g, 5.8 mmol) previously dissolved in dry THF (20 ml). The reaction was controlled by TLC and quenched by addition of ice containing ammonium chloride. After neutralization with aq. acetic acid and extraction with AcOEt, the organic layer was concentrated under reduced pressure. The residue was chromatographed on florisil (AcOEt/Hexane then AcOEt) to give the 1-C-phosphonate analogue **27** (60% yield). $[\alpha]_D$ + 34° (c = 1.13, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 5.76 (d, 1H, H-6, J_{5-6}=4), 4.77 (d, 1H, H-2, J_{2-3}=7); 4.53 (t, 1H, H-3, J_{3-2}=J_{3-4}=7); 4.0 (dd, 1H, H-5, J_{5-4}=7, J_{6-5}=4), 3.57 (t, 1H, H-4, J_{4-3}=J_{4-5}=8), 2.20 and 2.56 (d, 2H, H-7, H-7', $J_{7-7'}$=16); (Found: C, 61.69; H, 7.80; P, 6.61; $C_{24}H_{35}O_7P$ requires C, 61.79; H, 7.56; P, 6.64 %).

(Z / E), 4-*O*-Benzyl-2,3-*O*-cyclohexylidene-1,6-dideoxy-D-*myo*-inositol-1-vinyl(diethyl) phosphonate (28).

To a solution of tetraethyl methylene diphosphonate (1 ml, 4 mmol) dissolved in dry THF (10 ml), one crystal of bipyridyle and *n*-BuLi 1.4 N (2.9 ml) was added dropwise at 0°C until the appearance of a red color. The solution was stirred 30 mn. before addition of the cyclohexanone **1** (664 mg, 2 mmol) previously dissolved in dry THF (10 ml). The reaction was followed by TLC and quenched by addition of ice containing ammonium chloride. After neutralization with aq. acetic acid and extraction with AcOEt, the organic layer was concentrated under reduced pressure. The residue was chromatographed on florisil (AcOEt/Hexane) to give the phosphonate analogue **28** (70% yield, **E/Z** ratio = 3.5/1.5). **28E**: ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 5.98 (s, 1H, H-7), 4.53 (d, 1H, H-2, J_{2-3}=4), 4.26 (dd, 1H, H-3, J_{3-2}=4, J_{3-4}=6), 3.91 (m, 1H, H-5), 3.60 (dd, 1H, H-4, J_{4-3}=6, J_{4-5}=7), 2.62 and 3.09 (m, 2H, H-6a, H-6e); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 152.6 (C-1), 123.3 (C-7), 85.1 (C-3), 80.6 (C-4), 72.5 (C-2), 69.9(C-5), 39.3 (C-6); (Found: C, 61.69; H, 7.80; P, 6.61; $C_{24}H_{35}O_7P$ requires C, 61.79; H, 7.56; P, 6.64 %). **28Z**: ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 5.82 (s, 1H, H-7), 5.54 (d, 1H, H-2, J_{2-3}=5), 4.15 (dd, 1H, H-3, J_{3-2}=5, J_{3-4}=6), 3.46 (m, 2H, H-4, H-5), 2.20 and 2.56 (m, 2H, H-6a, H-6e); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 156.5 (C-1), 117.7 (C-7), 81.0 (C-3), 79.1 (C-4), 76.6 (C-2), 74.7 (C-5), 34.5 (C-6); (Found: C, 61.92; H, 7.35; P, 6.80; $C_{24}H_{35}O_7P$ requires C, 61.79; H, 7.56; P, 6.64 %).

2,3-*O*-Cyclohexylidene-1,6-dideoxy-D-*myo*-inositol-1-*C*-methylene(diethyl) phosphonate (29) and 2,3-*O*-Cyclohexylidene-1,6-dideoxy-D-*myo*-inositol-1-*C*-methylene(diethyl)-phosphonate-4,5-bis(dibenzyl) phosphate (30).

To a solution containing a mixture of derivative **28** (**Z/E**) (500 mg, 1.07 mmol) in AcOEt/EtOH (20 ml, 1/1 v/v) was added 5% Pd/C (500 mg) and the mixture was stirred for 2h under hydrogen pressure (75 psi). After filtration of the solid on Whatman paper (EtOH) and concentration to dryness of the filtrat, the crude product of the reaction **29** was submitted to the phosphorylation procedure using the phosphoramidite method to give the inositol phosphonate bis(dibenzyl)phosphate **30** (70% overall yield). $[\alpha]_D$ + 3.75° (c = 0.8, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ ppm: 4.5 (dd, 1H, H-4, J_{4-3}=8, J_{4-5}=9), 4.23 (m, 2H, H-2, H-5), 4.00 (dd, 1H, H-3, J_{3-2}=5, J_{3-4}=8), 2.06 (m, 2H, H-7, H-7'), 1.7 and 2.23 (m, 2H, H-6a, H-6e), 1.7 (m, 1H, H-1); ^{13}C NMR (50 MHz, $CDCl_3$) δ ppm: 82.3 (C-4), 78.5 (C-3), 75.7 (C-2), 75.4 (C-5), 32.0 (C-6), 29.4 (C-7), 29.4 (C-1); (Found: C, 60.38; H, 6.50; P, 10.53; $C_{45}H_{57}O_{13}P_3$ requires C, 60.12; H, 6.39; P, 10.33 %).

1,6-dideoxy-D-*myo*-inositol-1-*C*-methylene(diethyl)phosphonate-4,5-bisphosphate (31).

To a solution containing the intermediate **30** (200 mg, 0.22 mmol) in EtOH (2 ml, 1/1 v/v) was added 10% Pd/C (200 mg) and the mixture was stirred for 1h under hydrogen pressure (75 psi). After filtration of the solid on Whatman paper (H_2O), the filtrate was concentrated and TRIS salt (27 mg) was added in two instalments. The inositol analogue **31** was isolated by lyophilization as tetra-TRIS salt. ^1H NMR (400 MHz, D_2O): δ ppm: 4.23 (m, 1H, H-4), 4.15-4.05 (m, 5H, H-5, CH_2), 3.74 (sl, 1H, H-2), 3.62 (m, 1H, H-3), 2.14 to 1.97 (m, 3H, H-7'; H-6e; H-1), 1.9 (m, 1H, H-7), 1.67 (m, 1H, H-6a), 1.28 (m, 6H, $2CH_3$); ^{13}C NMR 50 (MHz, D_2O) δ ppm: 81.0 (C-4), 77.0 (C-5), 74.8 (C-2),73.2 (C-3), 64.7,64.5 (CH_2), 32.9 (C-6), 32.1 (C-1), 27.3 (C-7),16.9, 16.8 (CH_3).

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