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Synthesis of 1-*O*-(2-Oxo-Benzo-1,3,2-Dioxaphosphaocan-2-yl)-*Myo*-Inositol and 3,5-Dideoxy-1-*O*-(2-Oxo-Benzo-1,3,2-Dioxaphosphaocan-2-yl)-*Myo*-Inositol as Prodrugs of Inositolmonophosphatase Ligands.

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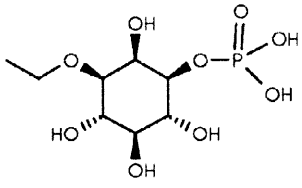
Abstract: 1-*O*-(2-oxo-benzo-1,3,2-dioxaphosphaocan-2-yl)-*myo*-inositol and 3,5-dideoxy-1-*O*-(2-oxo-benzo - 1,3,2 - dioxaphosphaocan - 2 - yl) - *myo* - inositol were prepared by selective modifications of *myo*-inositol. Phosphorylation used the phosphite method by means of the 2(*N,N*-di-isopropylamino)-benzo-1,3,2-dioxaphosphaocane.

The treatments of manic depression deseases by lithium salts are limited due to the low therapeutical index and the numerous side effects of these salts.[1-4] Consequently, it is of prime importance to find alternative therapies.[4,5] The lithium salts are uncompetitive inhibitors of the *myo*-inositol monophosphatase,[6-9] which is one of the enzymes involved in the inositol phosphate cycle.[10] Therefore, to design new inhibitors of this enzyme, structure activity relationship studies were developed around its natural substrates. With the help of the data obtained from X-Rays, NMR and modelling studies, it was possible to imagine the active site requirements of this enzyme, even if the mechanistic hypotheses remain plural.[11-16]



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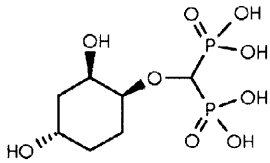

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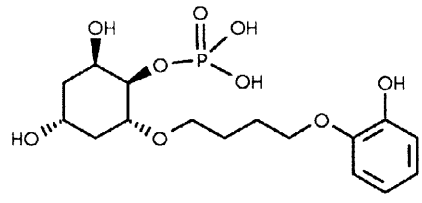

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Among the published structures, compounds **1-3** possess interesting inhibitory properties.[17-19] However, the ionic character and/or the high hydrophilicity of these molecules, probably, restrain their bioavailability.

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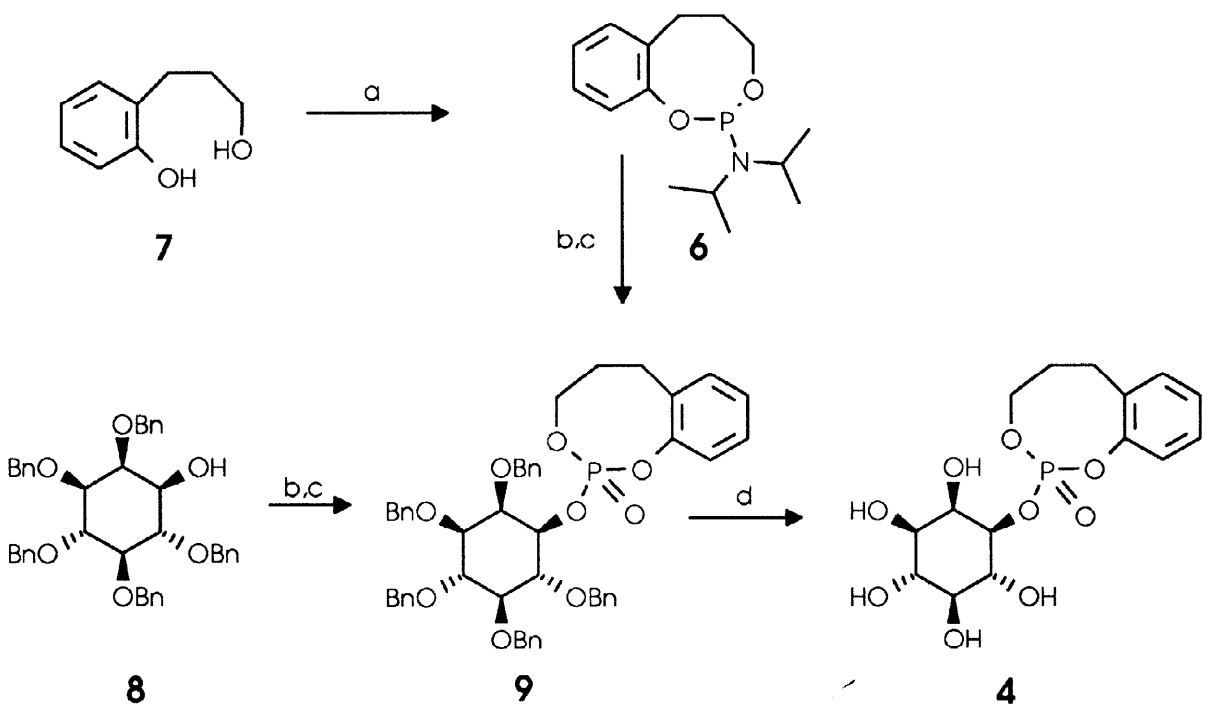
We report, here, the synthesis of 1-*O*-(2-oxo-benzo-1,3,2-dioxaphosphaocan-2-yl)-*myo*-inositol **4** and 3,5-dideoxy-1-*O*-(2-oxo-benzo-1,3,2-dioxaphosphaocan-2-yl)-*myo*-inositol **5**. These compounds can be considered as ligand prodrugs as the hydrolysis of the phenolic ester at physiological pH leads to a phosphate diester where the phenolic function could occupy the same space area in the enzyme active site as the phenol group of compound **3**. In addition, for compound **5** the non important hydroxyls are removed giving a less hydrophilic derivative. The protection of the ionic function and the lipophilicity increase could give potent and bioavailable inositol monophosphatase ligands.

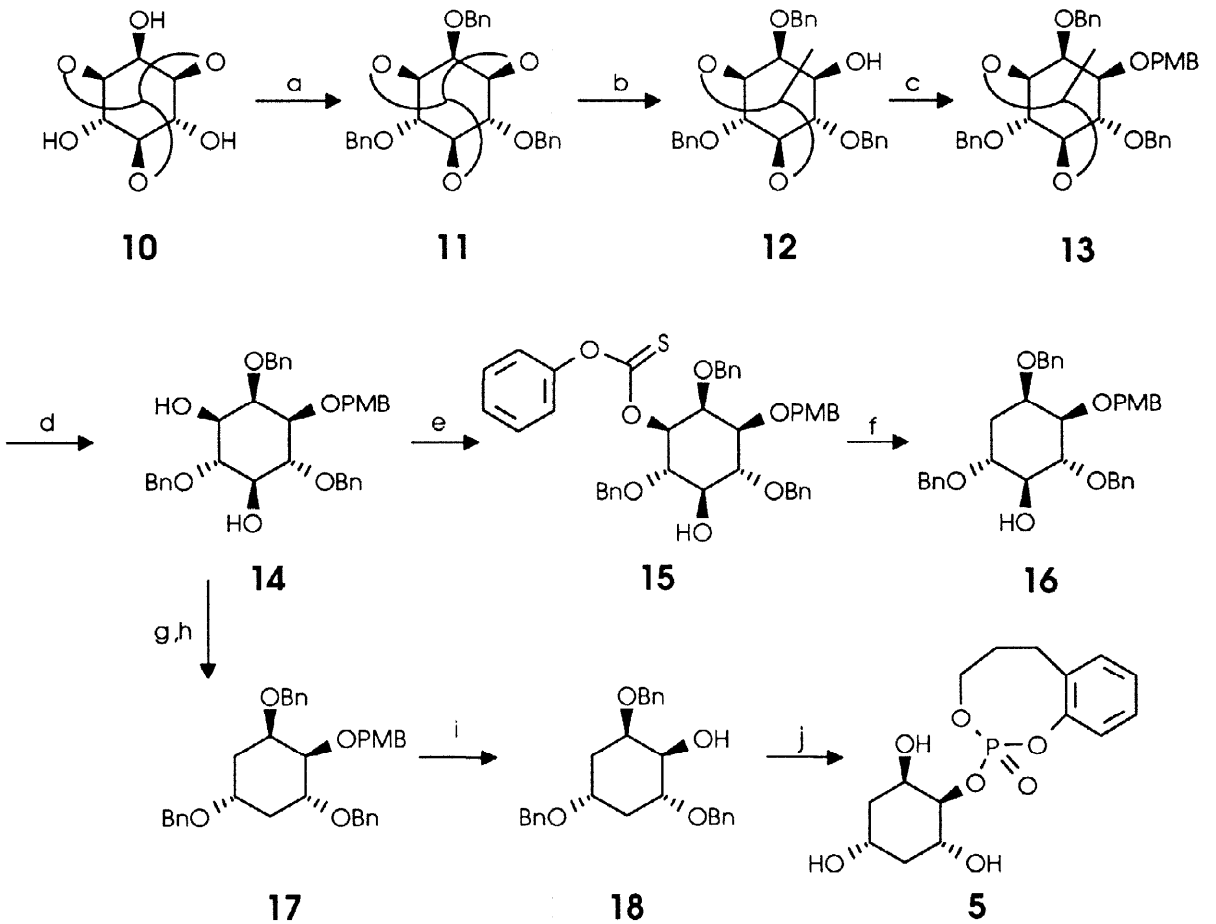
Scheme 1 shows the synthesis of 1-*O*-(2-oxo-benzo-1,3,2-dioxaphosphaocan-2-yl)-*myo*-inositol **4**. On one hand 2(*N,N*-di-isopropylamino)-benzo-1,3,2-dioxaphosphaocane **6**, was prepared starting from coumarin which was reduced to the diol **7** as previously described.[20] Treatment of the diol **7** with dichloro *N,N* di-isopropylphosphoramidite yielded[21] the expected reagent **6**. On the other hand, the pentabenzylated *myo*-inositol **8** was prepared in 6 steps using published procedures.[22,23] The phosphorylation of the last hydroxyl of **8** used the



Scheme 1: a) $Cl_2PN(iPr)_2$, 1 eq, THF, Et_3N, 2.4 eq, Ar, -78°C, 2h → RT, 16h, 69%; b) *1H*-tetrazole 2 eq, Ar, CH_2Cl_2, RT 5h; c) *m*-CPBA, 1.7 eq, CH_2Cl_2, -78°C, 15 min → RT, b+c 70%; d) H_2, Pd/C 10%, CH_2Cl_2-EtOH 2/5, 4 atm, RT, 12h, 75%.[25]

reagent **6** and 1*H*-tetrazole as catalyst to give an intermediate phosphite, which after oxidation with *m*-CPBA, furnished the protected final product **9**.[24] Removal of the benzyl protective group was made by hydrogenolysis using Pd/C as catalyst, giving compound **4**.[25]

The synthesis of the 3-5-dideoxy analogue **5** is given on scheme 2. The *myo*-inositol orthoester **10**[26] was tribenzylated to give the totally protected derivative **11**. Selective opening of the orthoester **11** with trimethylaluminium gave the ethylidene derivative **12**.[27] The free hydroxyl in position 1 was, then, protected as a *p*-methoxybenzyl ether (compound **13**). The next step was the removal of the ethylidene moiety by an acidic hydrolysis yielding the diol **14**. This diol, treated with phenylchlorothionoformate formed exclusively the 3-monothionocarbonate **15**.[28] Treatment with sodium hydride, carbon disulfide and methyl iodide followed by reduction via free radical fragmentation with tributyltinhydride in the presence of AIBN[29,30] yielded the expected dideoxy derivative **16**. The position 1 was,



Scheme 2: a) NaH, 3 eq, BnBr, 3 eq, DMF, Ar, 0°C, 2h → RT, 18h, 81%; b) $Al(CH_3)_3$, 8 eq, CH_2Cl_2, Ar, 0°C, 3h → RT, 4h, 87%; c) NaH, 3 eq, PMBCl, 2 eq, DMF, Ar, 0°C,1h, → RT, 14h, 98%; d) **13**, 2.1g, TFA, 5 ml, EtOH, 30 ml, H_2O, 5 ml, reflux, 2h, 93%; e) C_6H_5OCSCl, 2.6 eq, DMAP, 3.8 eq, MeCN, Ar, 0°C, 20h; f) Bu_3SnH, 3.5 eq, AIBN, reflux 4h, e+f 96%; g) NaH, 10 eq, THF, Ar, 0°C, 10 min → RT 30 min, CS_2, 30 eq, RT, 15 min → reflux 1h → RT, MeI, 10 eq, 15h, 91%; h) Bu_3SnH, 3eq, AIBN, toluene, reflux, 6h, 68%; i) HCl 3N, MeOH, reflux 1h 30 min 93%; j) see scheme 1, Bn = benzyl, PMB = *p*-methoxoybenzyl.[25]

then, selectively deprotected by an acidic hydrolysis giving the alcohol **18** which was phosphorylated and deprotected as described above to obtain the 3,5-dideoxy analogue **5**.[25]

Unfortunately, these two compounds did not exhibit any inhibitory activity toward human inositol monophosphatase.

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$\{^1H\}^{31}P$-NMR (300MHz); for **9** ($CDCl_3$): -4.09, -4.72; for **4** (CD_3OD): -4.52; for **5** as tribenzylether ($CDCl_3$): -4.59, -5.11; and for **5** (CD_3OD): -4.47.
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