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SYNTHESIS OF THIOPHOSPHATE ANALOGUES OF DL-*myo*-INOSITOL 1.2-CYCLIC PHOSPHATE

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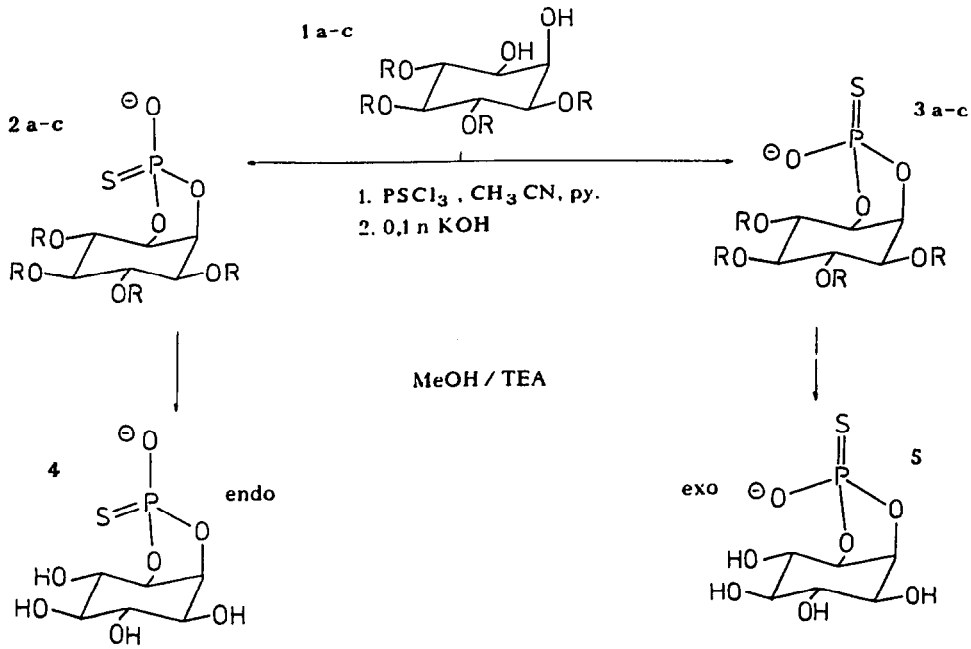
Summary: Pure diastereomers of DL-*myo*-inositol-1,2-cyclothiophosphate and their acetates, butyrates and benzylethers were synthesized by a new direct cyclothiophosphorylation method.

D-*myo*-Inositolpolyphosphates are second messengers for signal transduction of polar hormone action[1-3]. D-*myo*-Inositol 1.2-cyclic phosphate (IcP) is known to be an intermediate metabolite of phosphatidylinositol (PI) metabolism[4]. It is formed by hydrolysis of PI by phospholipase C[5]. The biological function of (IcP) has been proposed but never been proven[6]. Recently Saltiel et al. isolated a derivative of (IcP) from cultured myocytes and proposed it to be one of the second messengers of insulin action on cAMP metabolism[7].

Thiophosphate derivatives of natural occuring metabolites are powerful tools for the elucidation of enzyme mechanisms and metabolic pathways[8]. R_P - cAMPS e.g. acts as antagonist of cAMP metabolism[9]. By means of endo- and exo-uridine 2',3'-cyclophosphothioate the stereochemistry of ribonuclease was elucidated[10].

The synthesis of *myo*-Inositol 1.4.5-tristhiophosphate (IP_3S_3) by a phosphite approach has been described recently[11]. This thiophosphate was shown to be stable against phosphatases[12].

We report on the first synthesis of exo- and endo-DL-*myo*-inositol 1.2-cyclic thiophosphate **4**,**5**, their tetraacetates and tetrabutyrates respectively. The latters may be activated by metabolism. They are synthesized by direct cyclothiophosphorylation originally developed for the synthesis of R_P/S_P-cAMPS[13].



R: a = acetyl ; b = butyryl ; c = benzyl

To a solution of DL-1,4,5,6 -tetra-o-acetyl-*myo*-inositol **1a** (prepared by standard procedures[14]) in acetonitrile (40 mL) containing traces of pyridine, $PSCl_3$ (two mol equivalents) is added dropwise during 20 minutes at 35°C. The reaction mixture is poured slowly to a 0.1 n KOH solution in acetonitrile/water (v/v 1:1). After neutralisation with HCl and evaporation of the solvents the thiophosphate diastereomers **2a, 3a** were purified by flash chromatography (RP-8, 25-40µ, 22% MeOH/ TEAF-buffer (100mM)) to yield 10% of each diastereomer tetraacetate. The protecting groups were removed in TEA/MeOH (v/v 1:3)to give **4** and **5** . They precipitated quantitatively from the reaction medium by adding KCl.
All products were checked for diastereomeric purity by analytical hplc with RI-detection (compounds **2,3** : RP-18, 25% MeOH/ TEAF (100mM); **4, 5** : AXS, TEAF (100mM)).
All compounds were characterized by fab-ms spectra (neg.-mode), ^{31}P- and ^{1}H-nmr spectra . All ^{31}P-nmr shifts appeared between +71 and +75 ppm. Compounds **4b,c** and **5b,c** were prepared and characterized in the same manner. The hydrogenolysis of **2c,3c** with Pd / C (10%) is of no avail. Synthesis of pure enantiomers and polyphosphorylated cyclothiophosphates are on the way.

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