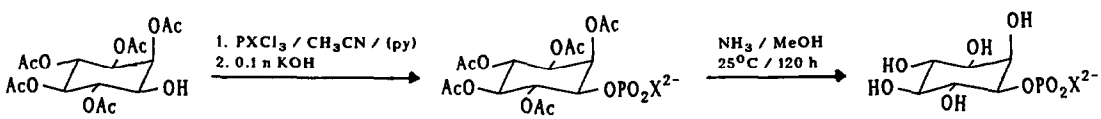
Tetrahedron Letters,Vol.29,No.32,pp 3921-3922,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

SYNTHESIS OF DL-*myo*-INOSITOL 1-PHOSPHATE AND ITS THIOPHOSPHATE ANALOGUE

Thomas Metschies, Carsten Schultz, Bernd Jastorff *
Department of Organic Chemistry, University of Bremen, D-2800 Bremen 33, FRG

Summary - A novel method for synthesis of *myo*-inositol 1-phosphate using phosphorus oxychloride is described an transferred to synthesis of its thiophosphate analogue.

The inhibition of *myo*-inositol 1-phosphatase (IP_1 -ase) by lithium ions is used therapeutically in treating manic-depressive illnesses [1,2,3]. IP_1 -ase is a key regulatory enzyme in phosphatidylinositol (PI) metabolism [4,5]. Interestingly this enzyme is not enantioselective [4]. Recently an anti-proliferative effect of lithium chloride on melanoma cells and its link to PI turnover was reported [6]. Non-hydrolysable derivatives of *myo*-inositol 1-phosphate **3** (IP_1) are potential inhibitors of the phosphatase and hence the phosphatidyl-inositol turnover. *myo*-Inositol 1-thiophosphate **5** might be a candidate for antagonistic action in PI metabolism. Conventional methods for synthesis of IP_1 [7,8] have failed for the thiophosphate. This prompted us to develop a novel method for synthesis of **3** which was transferred to thiophosphorylation later on.



Ac = CH_3CO
X = O, S

DL-1,2,4,5,6-Penta-O-acetyl-*myo*-inositol [1] was prepared from *myo*-inositol in a modified procedure [9] modelled on Angyal's method [10,11,12]. Treatment of **1** (12.8 mmoles) with phosphorus oxychloride (2.2 equivalents) in acetonitrile solution containing traces of pyridine for 1 h at 0°C, followed by hydrolysis with 0.1 N potassium hydroxide and removal of inorganic salts with methanol led to the crude product. The bis-triethylammonium salt of **2** was isolated by semipreparative hplc ion exchange chromatography on LiChroSorb AXS (Merck, Darmstadt) in more than 80% yield. As main by-products two isomeric tetra-acetates of **3** were identified (6, 7; 6 and 11% yield).

In order to remove the acetyl groups crude **2** (3.0 mmoles) was treated with ammonia-saturated methanol [13] at room temperature for 5 days. Almost pure DL-*myo*-inositol 1-phosphate [**3**] precipitated quantitatively from the reaction medium. After recrystallization from methanol **3** was obtained in 75% yield. IP_1 and its acetates were checked for purity by analytical hplc on AXS ion exchanger and characterized by fab-ms, ^1H-nmr and ^{31}P-nmr spectra (δ_P in D_2O: [**2**], bis-potassium salt +4.7 ppm, bis-triethylammonium salt -0.2 ppm; [**3**], bis-potassium salt +4.6 ppm).

The *myo*-inositol pentaacetate **1** can be thiophosphorylated with thiophosphoryl chloride using essentially the same procedure with the following modifications: prolonged reaction time and elevated temperature. More over the isolation of **4** followed the corresponding phosphate **2**. Unprotected *myo*-inositol 1-thiophosphate [**5**] precipitates quantitatively from ammonia methanol too and can be isolated in an overall yield of about 21 %. The thiophosphates were characterized by fab-ms (negative mode), ^1H-nmr and ^{31}P-nmr spectra (δ_P in D_2O: [**4**], bis-potassium salt +44.1 ppm; [**5**], bis-potassium salt +45.2 ppm). The products according to their ^{31}P-nmr spectra were free of the corresponding phosphates. Synthesis of other IP_1 analogues and the application of this procedure for synthesis of PI derivatives modified in the phosphate region are on the way.

Acknowledgement - We like to thank Dr.P.Schulze and I.Erxleben for fab-ms data and J.Stelten for nmr data. AXS ion exchanger material was generously supplied by Dr.Krebs, Merck AG, Darmstadt. Part of this work was supported by the Fonds der Chemischen Industrie.

REFERENCES

1 Schou M., in: Johnson F.N., Johnson S.(eds.), Lithium in Medical Practice, pp 21-39, University Press, Baltimore (1978).
2 Hallcher L.M., Sherman W.R., *J. Biol. Chem.* **255**, 10896 (1980).
3 Ackermann K.E., Gish B.B., Honchar M.P., Sherman W.R., *Biochem. J.* **242**, 517 (1987).
4 Parthasarathy R., Eisenberg jr. F., *Biochem. J.* **225**, 313 (1986).
5 Michell B., *Nature* **319**, 176 (1986).
6 Nordenberg J., Panet C., Wasserman L., Malik Z., Fuchs A., Stenzel K.H., Novogrodsky A., *Br. J. Cancer* **55**, 41 (1987).
7 Kiely D.E., Abruscato G.J., Baburao V., *Carbohydrate Res.* **34**, 307 (1974).
8 Molotkovsky J.G., Bergelson L.D., *Tetrahedron Lett.* **50**, 4791 (1971).
9 Tegge W., Schultz C., unpublished results (1986).
10 Angyal S.J., Tate M.E., Gero S.D., *J. Chem. Soc.* **1961**, 4116.
11 Angyal S.J., Tate M.E., *J. Chem. Soc.* **1965**, 6949.
12 Angyal S.J., Randall M.H., Tate M.E., *J. Chem. Soc.* (C) **1967**, 919.
13 Klyashchitskii B.A., Pimenova V.V., Shvets V.I., Preobrazhenskii N.A., *J. Org. Chem. USSR* **39**, 1622 (1969).

(Received in Germany 14 January 1988)