Tetrahedron Letters, Vol. 34, No. 44, pp. 7059-7060, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Synthesis of (±) *Myo*-Inositol-1-Q-Methylphosphonate-4,5-Bis(phosphate), an Analogue of D-*Myo*-Inositol-1,4,5-Tris(phosphate).

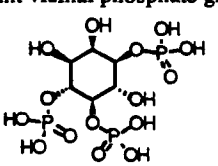
Laurent Schmitt, Bernard Spiess, Gilbert Schlewer*

Laboratoire de Pharmacochimie Moléculaire Faculté de Pharmacie de Strasbourg,
74 route du Rhin 67401 Illkirch France

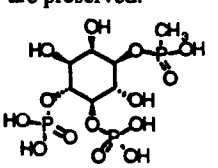
Abstract: The synthesis of (±) *myo*-inositol-1-Q-methylphosphonate-4,5-bis(phosphate) is reported. This compound is an analogue of D-*myo*-inositol-1,4,5-tris(phosphate) in which the phosphate group in position 1 is replaced by a methyl phosphonate function and where the important vicinal phosphate groups in positions 4 and 5 are preserved.

D-*myo*-inositol-1,4,5-tris(phosphate) **1** is a well-known intracellular second messenger that couples stimulation of external cell receptors to the release of intracellular calcium.[1,2]

Our physico-chemical studies around this compound showed the importance of the ionization state of this molecule for its affinity to the central receptors.[3-5] Within the framework of structure-activity relationship studies we have tried to introduce some modulation in the ionization state of inositol-phosphates and we were interested in the synthesis of (±) *myo*-inositol-1-O-methylphosphonate-4,5-bis(phosphate) **2**. This compound is an analogue of D-*myo*-inositiol-1,4,5-tris(phosphate) in which the phosphate group in position 1 is replaced by a methyl phosphonate with only one ionizable acidic group and where the important vicinal phosphate groups in positions 4 and 5 are preserved.



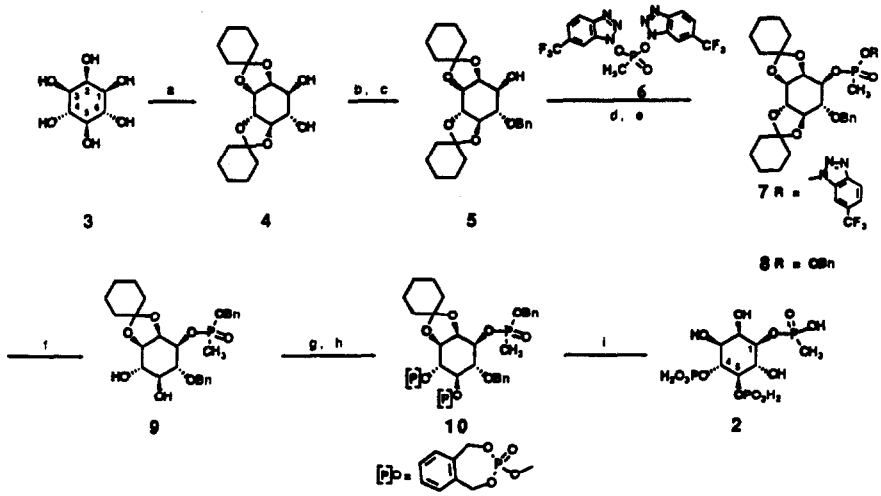
1



2

For this synthesis we have used *myo*-inositol **3** as starting material. The treatment with 1-ethoxycyclohexene in the presence of a catalytic amount of paratoluenesulfonic acid yielded a mixture of three racemic diacetals.[6] From this mixture racemic di-Q-cyclohexylidene-1,2-5,6-*myo*-inositol **4** was isolated by column chromatography on silica-gel with 22% yield. The diol **4** was selectively benzylated in position 4 by means of dibutyltinoxide. Thus the complex formed between the diol and the tin reagent was selectively opened in the presence of 2 equivalents of cesium fluoride[7,8] to give the alcohol **5**. The hydroxyl group in position 1, treated with bis(1-(6-trifluoromethyl)benzotriazolyl)-methylphosphonate[9] **6** yielded the intermediate **7** whose remaining benzotriazole moiety was immediately substituted to give the phosphonate **8**. The cyclohexylidene group in a *trans* junction on positions 4 and 5 was then selectively hydrolyzed using mild conditions[10] to generate the diol **9**. The diol was phosphitylated by means of diethyl amino-1,5-dihydro-2,3,4-benzo-dioxaphosphepine[11] in the presence of tetrazole. The intermediate bis(phosphite) was oxidized *in situ* in bis(phosphate) **10** by means of mCPBA.[11] Hydrogenolysis of **10**

removed the benzyl groups.[12] The liberated acidic groups allowed the removal of the last isopropylidene protective group yielding the expected (±) *myo*-inositol-1-O-methylphosphonate-4,5-bis(phosphate) **2** which was stabilized as cyclohexylammonium salt (Scheme).



Scheme: a: 1-Ethoxycyclohexene, pTsOH, DMF, 4h, 100°C, 22%; b: Bu_2SnO, toluene, 120°C, soxhlet molecular sieves 3A; c: BnBr, 2CsF, DMF, 20°C, 24h, 72% from 4; d: dioxane 20°C; e: BnOH, N-methylimidazole, 67% from 5; f: ethylene glycol, CH_2Cl_2, Amberlyst 77H, 20°C, 2h, 45%; g: N,N-diethylamino-1,5-dihydro-2,3,4-benzo-dioxaphosphepine, tetrazole, THF, CH_2Cl_2; h: *m*CPBA, CH_2Cl_2, -40°C then 20°C for 3h, 78% from 9; i: H2, Pd/C, ethanol 95%, 20°C, 12h, 57% after conversion in cyclohexylammonium salt.

More details concerning the physico-chemical investigations and the pharmacological studies will be reported elsewhere.

References and notes:

1 Streb, H.; Irvine, R.F.; Berridge, M.J *Nature*, **1983**, *306*, 67-69.
2 Berridge, M.J. *Nature*, **1993**, *361*, 315-325.
3 Schmitt, L.; Schlewer, G.; Spiess, B. *Biochem. Biophys. Acta* **1991**, *1075*, 139-140.
4 Schmitt, L.; Schlewer, G.; Spiess, B. *J. Inorg. Biochem.* **1992**, *45*, 13-19.
5 Schmitt, L.; Bortmann, P., Schlewer, G.; Spiess, B. (*J. Chem. Soc. Perkin Trans 1, in press*)
6 Garegg, P.J.; Iversen, T.; Johansson, R.; Lindberg, B. *Carbohydr. Res.* **1984**, *130*, 322-326.
7 Nagashima, N.; Ohno, M. *Chem. Lett.* **1987**, 141-144.
8 Murakata, C.; Ogawa, T. *Tetrahedron Lett.* **1990**, *31*, 2439-2442.
9 Dreef, C.E.; Dowes, M.; Elie, C.J.J.; van der Marel, G.A.; van Boom, J.H. *Synthesis* **1991**, 443-447.
10 Massy, D.R.; Wyss, P., *Helv. Chim. Acta* **1990**, *73*, 1037-1057.
11 Watanabe, Y.; Komoda, Y.; Ebisuya, K.; Ozaki, S., *Tetrahedron Lett.* **1990**, *31*, 255-256.
12 Angyal, S.J.; Tate, M.E., *J. Chem. Soc.* **1961**, 4122-4128.

(Received in France 29 July 1993; accepted 6 September 1993)