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Synthesis of (±) 1,2-Dideoxy-1,2-Diamino-*myo*-Inositol.

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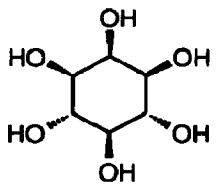
Abstract: Starting from *myo*-inositol, an isostere, diaminated in positions 1 and 2, was prepared. The key step of the synthesis was the simultaneous inversion of the dimesylate **6** with sodium azide leading to the global retention of the configuration.

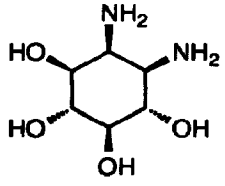
Myo-inositol **1** is the starting link of the inositol-phosphate cycle, and a large number of inositol derivatives are now well recognized for their biological properties[1-4].

Therapeutical effects could be modulated through modifications of the *myo*-inositol moiety. These structure-activity relationships may concern, modifications on the positions directly involved in the phosphorylation processes such as in the position 1, during the formation of phosphatidyl inositol[5]. other modifications concern the hydroxyl groups which seem implicated in the recognition of the phosphorylation or dephosphorylation active sites such as the position 2 for the 1-inositol monophosphatase[6,7].

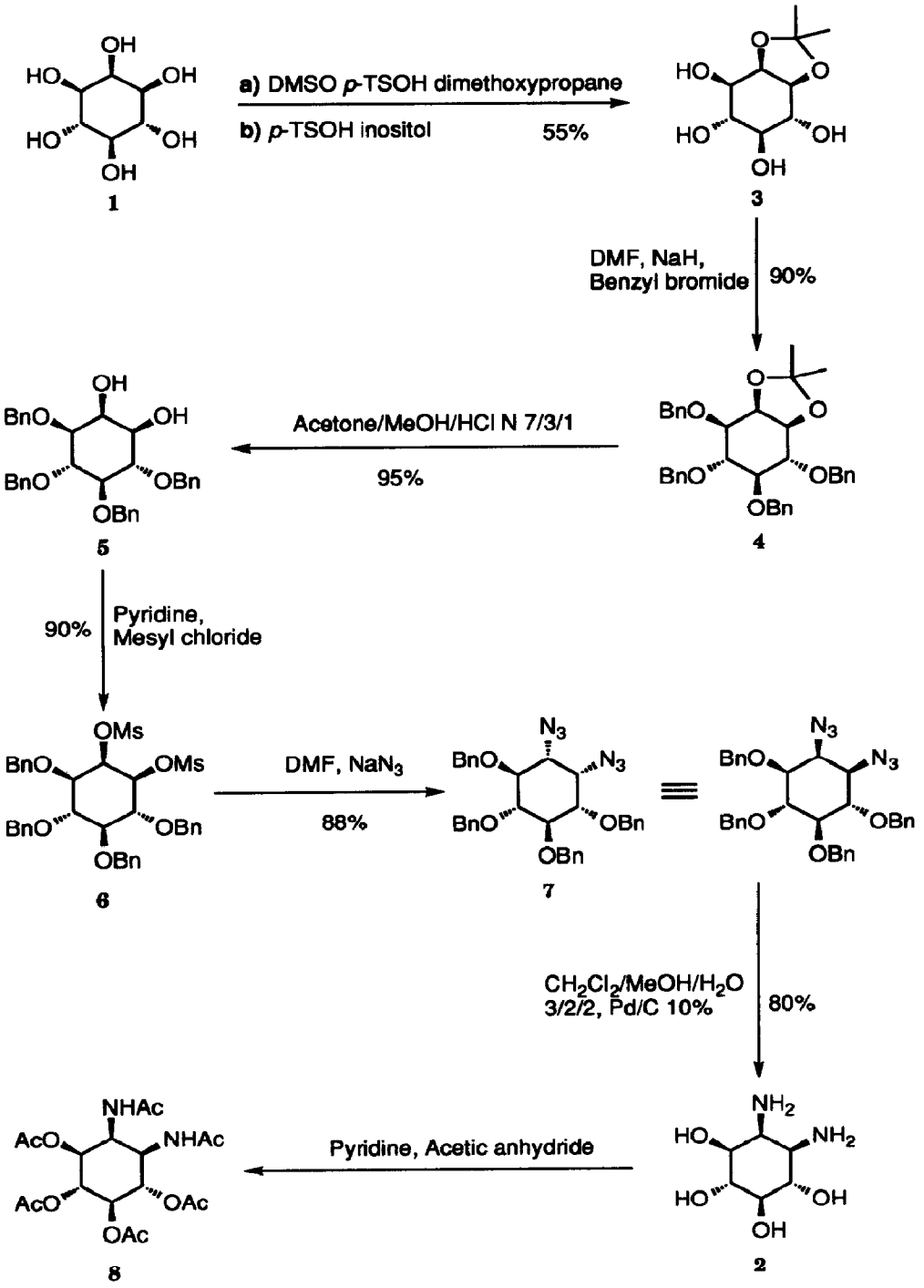
We were particularly interested in the synthesis of bioisosteres of *myo*-inositol and here we report the synthesis of an analogue **2** where the hydroxyl groups in positions 1 and 2 were replaced by primary amines.



1



2


a) DMSO p-TSOH dimethoxypropane
b) p-TSOH inositol
55%
DMF, NaH,
Benzyl bromide
90%
Acetone/MeOH/HCl N 7/3/1
95%
90%
Pyridine,
Mesyl chloride
DMF, NaN3
88%
CH2Cl2/MeOH/H2O
3/2/2, Pd/C 10%
80%
Pyridine, Acetic anhydride
1
2
3
4
5
6
7
8

The starting material for this synthesis was *myo*-inositol **1**. Treatement of **1** with 2,2-dimethoxypropane in DMSO in the presence of a catalytic amount of *p*-TSOH gave transitorily three racemic di-*O*-isopropylidene derivatives[8]. The 2,2-dimethoxypropane was completely evaporated ; then, the same amount of the starting *myo*-inositol was added into the crude mixture inducing a transacetalysation which selectively deprotects the *trans* fused acetals of the inositol nucleus. This resulted in the exclusive formation of the monoisopropylidene **3** with an overall yield of 55%[8]. The four hydroxy groups were then benzylated by treatement of the corresponding alcoolate, formed by means of NaH, with benzyl bromide[9] yielding the totally protected inositol **4**. The 1,2-*cis*-isopropylidene protective group was hydrolyzed by treatement with HCl[9] to give the diol **5** which was transformed to the corresponding dimesylate[10] **6** with a 90% yield.

The next step was the key reaction of this synthesis. Thus, the simultaneous inversion at the positions 1 and 2 by substitution of the mesylates, by means of sodium azide[10], lead to the dideoxy diazide[11] **7** resulting on the overall retention of the *myo*-inositol configuration. This is due to the particular geometry of the *myo*-inositol. Thus, after substitution, the position 1 was inverted from an equatorial orientation to an axial one, hence this position turned into the new position 2; and the position 2 was inverted from an axial orientation to an equatorial one, and became the new position 1. Hydrogenolysis at 5 atm using Pd/C as catalysator[12] allowed the simultaneous reduction of the azides into amines and deprotection of the benzyl ethers to give the title compound[13] **2**. To characterize the final product it was converted to its hexaacetyl-derivative[14] **8**, and it was submitted to a FAB mass spectrometric analysis[15].

This diamino-isostere could be a potential competitor for *myo*-inositol in the inositol- phosphates cycle. It would be interesting to attempt the cellular biosynthesis of the the diamino cyclitol by phosphatidylinositol synthase into modified phosphoinositides, as well as its membrane permeability.

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(11) For the assignement of the NMR signals a bidimensional COSY 90 experiment has been used. ^{1}H-RMN ($CDCl_3$): 7.4-7.2(*m*, 20H, -(CH_2-C_6H_5)$_4$), 5.0-4.7(*m*, 8H, -($CH_2C_6H_5$)$_4$), 3.98(*t*, J=3.3, 1H, *H*-2) 3.88(*d*, J=9.5, 1H, *H*-6), 3.79(*d*, J=9.5, 1H, *H*-4), 3.56(*dd*, J=9.5 and J=3.2 1H, *H*-1) 3.47(*t*, J=9.3, 1H, *H*-5), 3.37(*dd*, J=10.0 and J=3.2, 1H, *H*-3).
IR (CH_3Cl): 2103 cm^{-1} (N_3).

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(13) ^{1}H-RMN (D_2O): 3.80(*t*, J=9.5, 1H), 3.62(*t*, J=10.6, 1H), 3.5-3.1(*m*, 4H).

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(15) Mass Spectrum: m/z (FAB$^+$) 431 (MH$^+$, 62%), 371 (11), 313 (11), 182 (23), 149 (100).

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