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Synthesis of (±)-4-deoxy-4-fluoro-*myo*-inositol

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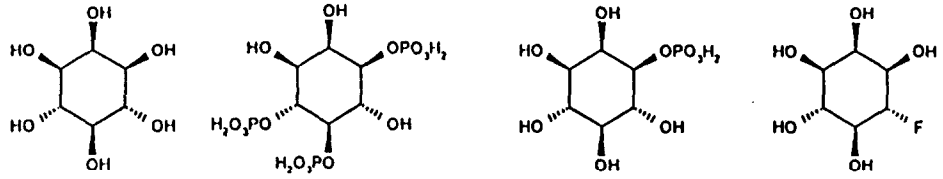
Abstract. 4-Deoxy-4-fluoro-*myo*-inositol was prepared by means of DAST with retention of configuration due to the assistance of a neighbouring benzyl ether.

Myo-inositol **1** is the starting material for numerous biosyntheses leading particularly to inositol-phosphates, such as *myo*-inositol 1,4,5-tris(phosphate) **2** which possesses second messenger properties[1] or *myo*-inositol 1-monophosphate **3** which is a lead compound in manic depression research.[2,3] The position 6 seems to play an important role in the respective mechanisms of action. Thus, the ionization state of **2** has been correlated with its binding to brain membranes,[4,5,6] the position 6 could help to stabilize the active ionization state through hydrogene bounds. The position 6 of the monophosphate **3** seems to be implicated in a mechanistic site of the dephosphorylating enzyme.[7,8]



1 **2** **3** **4**

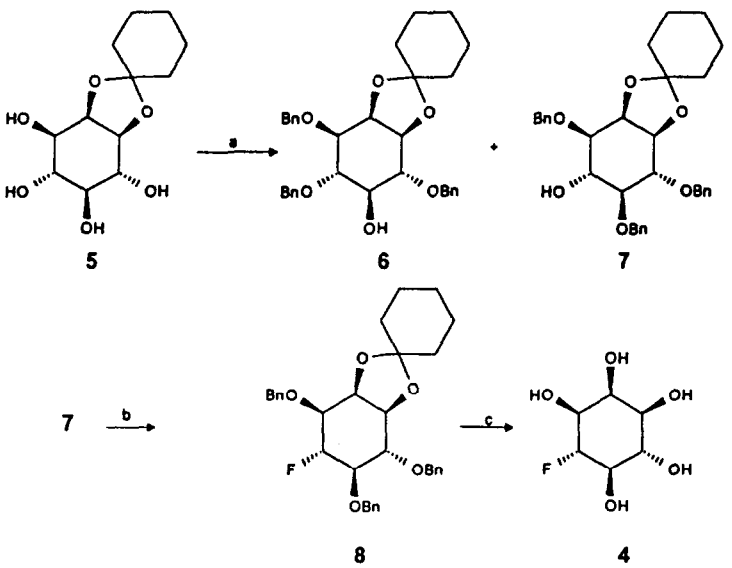
Due to the presence of highly charged groups, inositol-phosphates can difficultly cross the biological membranes.

The synthesis of inositol analogues keeping the *myo* configuration and able to modulate the effects of the position 6 are of prime interest. Fluorinated analogues of *myo*-inositol-phosphates have been reported for their biological properties.[9,10,11,12,13]

We want to report the synthesis of 4-deoxy-4-fluoro *myo*-inositol **4** which could be a bioprecusor of the corresponding phosphates.

The starting material of the synthesis was (±)-1,2-*O*-cyclohexylidene *myo*-inositol **5** prepared by well known methods.[14] Treatment of the tetraol **5** with benzyl bromide in the presence of dibutyltin oxide and tetrabutylammonium bromide, using the conditions published by Gigg *et al*[15], gave a 1/1 mixture of the two tri-*O*-benzyl derivatives **6** and **7** (Scheme). Treatment of the (±)-3,5,6 tribenzyl derivative **7** with DAST[11,12] afforded (±)-4-deoxy-4-fluoro-3,5,6-tri-*O*-benzyl-1,2-*O*-cyclohexylidene *myo*-inositol **7** identified by proton and fluoride NMR[16]. This was an interesting case where the use of DAST led to retention of configuration. Such retentions of configurations have been observed and required the assistance of neighbouring groups, which, in our case was a benzyl group.[17,18] Removal of the protective groups by hydrogenolysis in a slightly acidic medium gave the expected fluoro derivative **4**.

This reaction with retention of configuration will be used for the synthesis of fluorinated analogues of other inositols and related compounds



Scheme : Synthesis of 4-deoxy-4-fluoro myo inositol a: BnBr, Bu_2SnO, Bu_4NBr; b: DAST; c: H_2,Pd/C,H^+,MeOH, H_2O

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[16] Compound **8**: ^{1}H-RMN ($CDCl_3$ / C_6D_6 ; 25 : 75, 300 MHz): 7,5-7,2 (*m*, 15H, -(C_6H_5)); 5,0 (*dt*,1H, $^2J_{H_4F}$ = 51,2, $^3J_{H_4H_3}$ = $^3J_{H_4H_5}$ = 8,1); 4,9-4,6 (*m*, 6H, -(CH_2-C_6H_5)3); 4,18 (*ddd*, $^3J_{H_2H_1}$ = 5,6, $^3J_{H_2H_3}$ = $^3J_{H_2F}$ = 4,0, 1H, *H2*); 3,97 (*t*, H, $^3J_{H_1H_2}$ = $^3J_{H_1H_6}$ = 6,2, *H1*); 3,77 (*dd*, $^3J_{H_6H_5}$ = 8,6, $^3J_{H_6H_1}$ = 6,4, 1H, *H6*); 3,62 (*ddd*, $^3J_{H_3F}$*cis* = 11,3, $^3J_{H_3H_4}$ = 8,7, $^3J_{H_3H_2}$ = 3,8, 1H, *H3*); 3,46 (dt, $^3J_{H_5F}$*cis* = 16,2, $^3J_{H_5H_4}$ = 8,1, $^3J_{H_5H_6}$ = 8,1, 1H, *H5*); 1,8-0,7 (*m*, 10H, -(C_6H_{10})). ^{19}F-RMN ($CDCl_3$) : -195.72 (*dddd*, $^2J_{H_4F}$ = 51,2, $^3J_{H_5F}$*cis* = 16,2, $^3J_{H_3F}$*cis* = 11,3, $^3J_{H_2F}$ = 4,0, 1F, *F4*).

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