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SYNTHESIS OF PROTECTED *myo*-INOSITOLS

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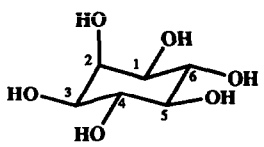
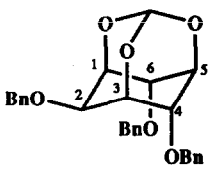
Summary: Regioselective cleavages of the myo-*inositol monoorthoformate (2) and a rearrangement of the acetal (5) are reported.*

Inositol phosphates have recently been shown to be important in the regulation of cell action.[1] The mechanisms by which inositol phosphates are produced, and subsequently metabolised, are not fully understood. Control of phosphoinositide metabolism could lead to the treatment of various diseases. As a result there has been a large amount of interest in synthesising inositol phosphates,[2] phosphatidyl inositols,[3] and their analogues.

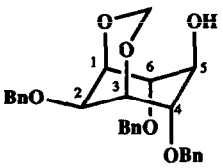
Most approaches to the synthesis of inositol phosphates have started from *myo*-inositol (**1**).[2] This requires selective protection of the hydroxyl groups for which several methods have been developed. Some of these suffer from the disadvantage of low yield and or difficult separation of isomers.[2]



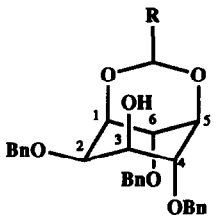
(1)



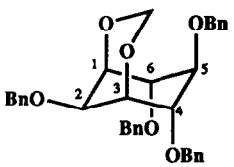
(2)



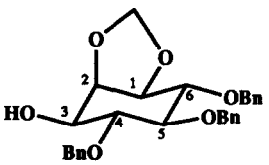
(3)



(4)
a. R = H
b. R =Me



(5)



(6)

We have discovered several methods to synthesise protected *myo*-inositols in high yield. Our starting point was the 2,4,6-tri-*O*-benzyl orthoester (**2**).[4] We were interested to know if the orthoester could be selectively cleaved to give either the 1,3-acetal (**3**) or the 1,5-acetal (**4**), both of which could be useful in syntheses of inositol phosphates.

Treatment of the orthoester (**2**) with DIBAL in dichloromethane and hexanes at room temperature for 2.5 hours gave a highly stereoselective cleavage of the orthoester (**2**) to produce the 1,3-acetal (**3**) together with a trace of the isomer (**4a**) [**3**:**4a** ~ 20:1] in high yield (93-100%). Two equivalents of DIBAL were required for complete reaction. Use of one equivalent of DIBAL led to a yield of 47% of acetal (**3**) and 25% starting material after 2 days. Stork[5] has reduced a bicyclic orthoester with borane as a key step in his synthesis of (+)-(9*S*)-dihydroerythronolide A, while Yamamoto[6] has studied the reductive cleavage of monocyclic orthoesters with DIBAL.

Treatment of the orthoester (**2**) with 2.5 equivalents of trimethylaluminium gave the alkylated 1,5-acetal (**4b**) in high yield (84-86%). It is noteworthy that trimethylaluminium and DIBAL caused opposite selectivities in cleavage of this orthoester, and it is possible that the size of the reagent can explain the selectivities obtained.

Benzylation of the alcohol (**3**) gave the tetra-*O*-benzyl derivative (**5**) in high yield (97-99%). Reaction of this compound with titanium(IV) chloride at -78 °C in dichloromethane gave specific monodebenzylation and acetal migration to furnish the rearranged acetal (**6**) (m.p. 105-106.5 °C) (63-71%). Hori *et al.*[7] have reported highly regioselective de-benzylation of carbohydrates. They propose that the Lewis acid coordinates specifically to three ether-oxygens. A highly ordered complex of this nature could be invoked for (**5**) as well.

In summary, this Letter reports concise and high yielding routes to differentially protected *myo*-inositol derivatives. The protected inositols should be useful in the synthesis of various inositol phosphates (such as *myo*-inositol 1,3-bisphosphate and *myo*-inositol 1-phosphate). Further details of the applications and mechanisms of formation of these intermediates will be reported in a full paper.[8]

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1 See for example, 'Inositol Lipids and Transmembrane Signalling,' The Royal Society, London, 1988; C. P. Downes, *Biochem. Soc. Trans.*, 1989, **17**, 259.

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8 All compounds are either *meso* or racemic and exhibited satisfactory spectroscopic and analytical data.

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