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APPROACHES TO THE SYNTHESIS OF GLYCOSYL PHOSPHATIDYL INOSITOLS. ENANTIOSELECTIVE SYNTHESIS OF OPTICALLY ACTIVE *chiro*- AND *myo*-INOSITOLS.

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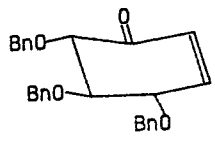
Abstract: An efficient synthetic strategy to optically active conveniently substituted D-*chiro* (**5**) and D-*myo*-inositol (**10**) derivatives has been developed starting from methyl α-D-glucopyranoside. Compounds **5** and **10** constitute valuable intermediates for the preparation of glycosyl phosphatidyl inositols.

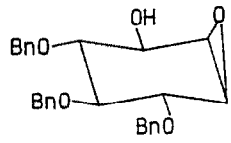
Although the molecular events involved in the biological action of insulin remain poorly understood, it has been reported that the binding of the hormone to its receptor promotes the phosphodiester hydrolysis of a glycosyl phosphatidyl inositol and releases diacyl glycerol and the polar head group of this lipid.[1] This polar head group is a phosphooligosaccharide containing *myo*- or *chiro*-inositol 1-phosphate, glucosamine, and galactose,[1,2] and mimics insulin directed effects on protein phosphorylation-dephosphorylation as well as a variety of the biological effects of the hormone.[3] The structure of this substance has not been completely elucidated but present data seem to indicate it to have many features in common with the glycosyl phosphatidyl inositol anchors of a number of cell membrane proteins.[4] D-*myo*-Inositol appears in this anchors phosphorylated at position 1 and glycosylated at position 6 by a complex glycan.[5]

Approaches to the synthesis of these molecules have recently appeared.[6] The synthesis of the conveniently functionalized inositol moiety has been achieved starting from *myo*-inositol through quite a number of conventional hydroxyl protection and deprotection steps, with the added disadvantage of racemic resolution at any stage of the synthetic scheme. We now report syntheses of conveniently functionalized enantiomerically pure *chiro*- and *myo*-inositol derivatives as useful intermediates for the synthesis of these complex glycosyl phosphatidyl inositols.

Methyl α-D-glucopyranoside was converted into enone **1** in multigram amounts using well-known chemistry,[7] and compound **1** further transformed into the key epoxide **2** as recently reported by us.[8] Acid-catalyzed opening[9] of the epoxide ring afforded the *chiro*-inositol derivative **3** (75%), the stereochemistry of which was unequivocally established by transformation [1) BnBr/NaH/DMF; 2) Pd-C/*p*-TsOH/EtOH/reflux; 3) MeI/NaH/DMF; 4) H_2/Pd-C/MeOH-EtOAc] into the previously known[10] 1-D-1-*O*-methyl-*chiro*-inositol (**4a**) and the penta-*O*-acetate (**4b**). Tin mediated regioselective benzylation of **3** gave **5** (83%), a 1-D-*chiro*-inositol derivative in which positions 1 and 6 appear differentiated for further phosphorylation and glycosylation. Similar *p*-methoxybenzylation of **3** gave **6** (80%).



1



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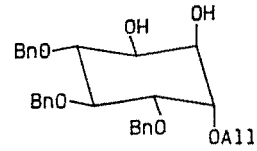
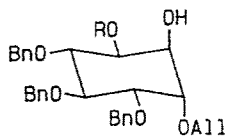
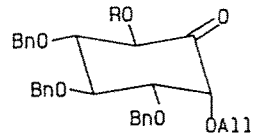


3

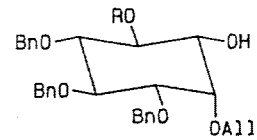
Attempts to invert the axial hydroxyl group of **5** conventionally either through a Mitsunobu reaction[11] or by treatment of the corresponding triflate with benzoyl nucleophiles[12] did not afford the desired *myo*-inositol derivative. Oxidation of either **5** or **6** (PCC/CH_2Cl_2) gave ketones **7** or **8** (80-85%) whose reduction seemed to be strongly dependent on steric and electronic factors (Table 1). Lithium reagents seem to favour α-attack of hydride and only with very large alkyl substituents in the reducing agent was the needed stereochemistry (ß-attack) obtained. Most likely, the configuration of the hydroxyl groups α to the carbonyl function in **7** and **8** allows complexation of these molecules by both faces. The stereochemistry of **10** was unequivocally demonstrated by conversion [1) MeI/NaH/DMF; 2) Pd-C/*p*-TsOH/EtOH-EtOAc/reflux; 3)H_2] into the previously known[13] (-)-D-bornesitol (**11**) and its penta-*O*-acetate (**12**). Compound **10** is a conveniently substituted 1-D-*myo*-inositol derivative in which positions 1 and 6 appear differentiated for further phosphorylation and glycosylation.



5 R=Bn
6 R=PMBn



7 R=Bn
8 R=PMBn

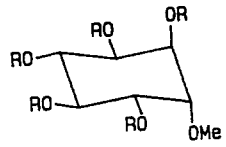


9 R=Bn
10 R=PMBn

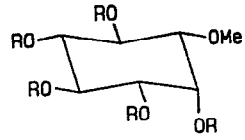
Table 1

Entry	R	[H]	Solvent	t(°C)	Yield (%)	9:5 (or 10:6)[a]
1	Bn, PMBn	$NaBH_4/CeCl_3$	MeOH	-78	86	1 : 1
2	Bn	L-Selectride	THF	-78 → rt	-[b]	1 : 7
3	Bn	$LiBH_4$	THF	-78	-[b]	1 : 7
4	Bn, PMBn	$LiAlH_4$	THF	-78	-[b]	1 : 2.2
5	Bn, PMBn	$LiAl(O^tBu)_3H$	THF	-78	-[b]	1 : 2.0
6	PMBn	$LiAl(O^tBu)_3H/HgCl_2$	THF	-78	-[b]	1 : 2.7
7	PMBn	(R)-Alpine hydride[14]	THF	-90	77	6 : 1
8	PMBn	(S)-Alpine hydride[14]	THF	-90	-[b]	5 : 1

[a] Determined by ^{1}H-N.m.r.
[b] Not determined.



4 a R= H
b R= Ac



11 R= H
12 R= Ac

The synthetic strategy here reported constitutes a high yielding and convenient procedure for the preparation of enantiomerically pure synthetic intermediates in sufficient amounts as to permit further elaboration towards the glycosyl phophatidyl inositols involved in insulin action and in the anchoring of cell membrane proteins.

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