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SYNTHESIS OF L-*CHIRO*-INOSITOL-1,2,3-TRISPHOSPHATE AND -1,2,3,5-TETRAKISPHOSPHATE BY FERRIER REACTION OF METHYL α-D-MANNOPYRANOSIDE

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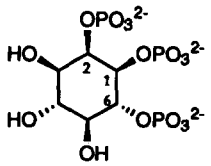
Abstract: The Ferrier rearrangement of a methyl α-D-mannopyranoside derivative (**8a**), followed by a stereoselective reduction gave a L-*chiro*-inositol derivative (**2**), which was converted to L-*chiro*-inositol 1,2,3-trisphosphate (**3**) and L-*chiro*-inositol 1,2,3,5-tetrakisphosphate (**4**). Compounds **3** and **4** may be considered to be the C3-position stereoisomers of D-*myo*-inositol 1,2,6-trisphosphate (α-trinositol) and D-*myo*-inositol 1,3,4,5-tetrakisphosphate, respectively, and should be useful for the binding studies with their macromolecular counterparts.

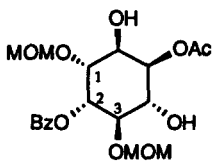
The phospholipase C catalyzed cleavage of membrane bound phosphatidylinositol bisphosphate (PIP_2) to produce 2nd messenger molecules, *myo*-inositol-1,4,5-trisphosphate ($InsP_3$) and diacylglycerol, is a crucially important event in cellular signalling processes.[1] A number of other *myo*-inositol phosphates have also been implicated as either second messengers or key metabolic intermediates in the intracellular signal transduction pathways.[2] *myo*-Inositol 1,2,6-trisphosphate (α-trinositol; PP56) was shown to have an inhibitory effect on the neuropeptide Y-evoked vasoconstriction in many vascular assays and also to be a potent anti-inflammatory agent, but not to possess an appreciable agonist activity.[3] More recently it has been suggested that α-trinositol has specific and possibly unique binding sites in the membranes from several types of rat tissues, although it shares common binding characteristics with Ins(1,3,4,5)P_4 and, to a lesser degree, also with $InsP_6$ and Ins(1,4,5)P_3.[3e]

As a part of our efforts to understand the molecular recognition aspect of the inositol phosphate-dependent signal transduction entailing phospholipase C, Ins(1,4,5)P_3 rececptor and the metabolic enzymes, we have been studying syntheses and biological activities of various natural and unnatural inositol phosphates and their structural analogues.[4] In general, synthesis of modified *myo*-inositol phosphate derivatives might be conveniently carried out with *myo*-inositol as the starting material, but this route suffers from the inherent disadvantage of having to resolve the racemate at some suitable stage of the synthesis, if an optically active compound is desired. Use of chiral natural products as the starting material has obvious advantages in this regard.[5] The Ferrier reaction has successfully been employed for the synthesis of chiral *myo*-inositol derivatives from D-glucose derivatives.[4a,6] We envisioned that the Ferrier procedure might be analogously applied to the D-mannose derivatives in the preparation of L-*chiro*-inositol derivatives, which could be potentially useful in the molecular recognition studies as the C3-position stereoisomers of the corresponding *myo*-inositol derivatives. Herein we report the first such synthesis of L-*chiro*-inositol derivatives, **2**, **3**, and **4** starting from methyl α-D-mannopyranoside (**5**).

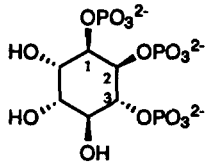
On the basis of the known mechanism of the Ferrier rearrangement,[6,7] it was expected that the enol acetate derived from methyl α-D-mannopyranoside should yield a L-*chiro*-inositol derivative, because the



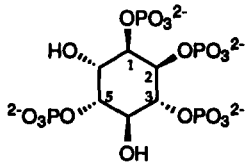
1. α-trinositol (PP56)



2



3



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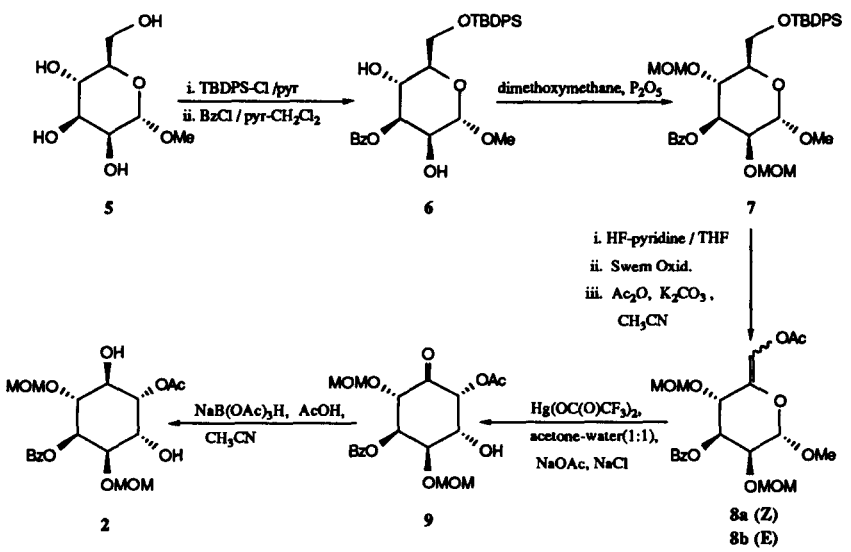
opposite stereochemistry at the 2-positions of D-mannopyranoside and D-glucopyranoside was not likely to seriously affect the stereochemistry of the two new chiral centers generated in the Ferrier rearrangement. Our synthetic plan (Scheme 1 and 2) required selective protections of various hydroxyl groups prior to the Ferrier rearrangement. Thus, methyl α-D-mannopyranoside (**5**) was converted to methyl 3-*O*-benzoyl-6-*O*-(*t*-butyldiphenyl)silyl-α-D-mannopyranoside (**6**) by successive treatments with 1.2 equiv. of (*t*-butyldiphenyl)silyl chloride (TBDPS-Cl) in pyridine[8] and then 1.0 equiv. of benzoyl chloride in CH_2Cl_2 (64 % in two steps). When more than 1 equiv. of benzoyl chloride was used in the benzoylation, a considerable amount of undesired 2,3-dibenzoate was produced. Although with the triphenylmethyl ether protection of the 6-OH group, the selective 3-*O*-monobenzoylation could be much more easily achieved, the trityl protection was not compatible with the present synthetic scheme. The remaining two secondary hydroxyl groups of **6** were protected as methoxymethyl (MOM) ether with dimethoxymethane. Contrary to the literature report,[9] use of lithium bromide as the catalyst was not effective in this protection procedure. But, it was found that the addition of 3.0 equiv. of P_2O_5[10] to the mixture of **6** and dimethoxymethane (15 eq) smoothly effected the formation of the fully protected methyl α-D-mannopyranoside derivative (**7**, 94%). Desilylation of **7** (86%) with 70% HF-pyridine,[11] followed by Swern oxidation (DMSO, oxalyl chloride,

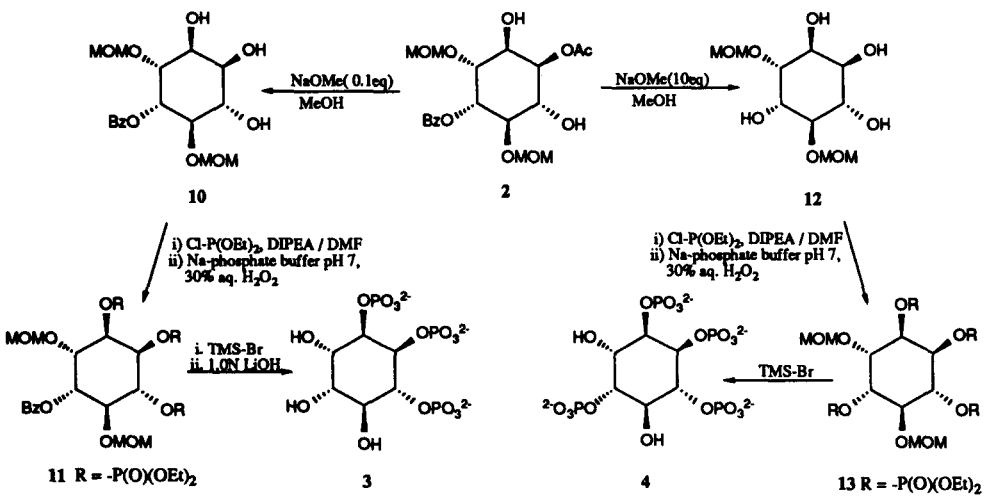
Scheme 1.



triethylamine, -78 °C),[12] and enol acetylation (4 eq. K_2CO_3, 4 eq. Ac_2O, acetonitile, 60°C), gave in 86% over the two steps the desired enol acetate (**8a**(Z) : **8b**(E) = 4 : 1), which were separated on silica-gel.[13] Treatment of the enol acetate (**8a**) with mercury trifluoroacetate (1.2 eq), NaOAc (1.2 eq) and NaCl in acetone-water (4 : 1)[6b] exclusively gave the desired L-*chiro*-inososе (**9**) in 66% isolated yield, and no other stereoisomer was detected.[14] Selective reduction of **9** with 10 eq. $NaB(OAc)_3H$ in AcOH and acetonitrile[15] gave L-*chiro*-inositol derivative (**2**) in 73 %.[14]

With L-*chiro*-inositol derivative (**2**) in hand, we continued on the synthesis of **3** and **4** as shown in Scheme 2. Treatment of **2** with 0.1 equiv. of NaOMe in MeOH at rt for 1 hr gave 5-*O*-benzoyl-4,6-di-*O*-methoxymethyl-L-*chiro*-inositol (**10**, 64 %), while use of a large excess of sodium methoxide gave 4,6-di-*O*-methoxymethyl-L-*chiro*-inositol (**12**, 10 eq. NaOMe, MeOH, rt, 5 hr, 81 %). Phosphitylation and subsequent oxidation ($(EtO)_3P$-Cl , $(iPr)_2NEt$, DMF, rt, 4 hr; 30% aq. H_2O_2, 1N aq. sodium phosphate buffer (pH 7), rt, overnight)[4h,i] of **10** and **12** gave the fully protected trisphosphate (**11**, 99%) and tetrakisphosphate (**13**, 73%), respectively. ^{31}P-nmr spectra showed their characteristic peaks at δ -0.418, -0.781, and -1.535 ppm for the trisphosphate (**11**), and at δ -0.474, -0.921, -1.005, and, -1.479 ppm for the tetrakisphosphate (**13**). Finally, successive treatments of **11** with TMS-Br and LiOH for the removal of protecting groups, followed by ion exchange on Dowex 50X8-100 (H^+ form), pH adjustment to 10 with LiOH, and lyophilization gave L-*chiro*-inositol 1,2,3-trisphosphate (**3**). Deprotection of **13** with a large excess amount of TMS-Br, followed by evaporation of all volatile material, and pH adjustment to 10 with LiOH provided L-*chiro*-inositol 1,2,3,5-tetrakisphosphate (**4**).[16]

Scheme 2.



In summary, we have successfully developed a synthetic route to optically active L-*chiro*-inositol derivatives **3** and **4** by means of the Ferrier rearrangement of a D-mannoside derivative (**8a**). Although this methodology requires selective masking and unmasking of the non-participating hydroxyl groups of the sugar, it represents a much more efficient synthesis of L-*chiro*-inositol 1,2,3,5-tetrakisphosphate (**4**), which had previously been synthesized from L-quebrachitol.[5b] The binding studies of compounds **3** and **4** with

α-trinositol and other $InsP_n$ receptors and their metabolic enzymes are currently in progress.[17]

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13. **8a** : 1H-nmr ($CDCl_3$): δ 8.1-7.4 (m, 5H, Ar-H), 7.11 (d, J =1.2, 1H, vinyl-H), 5.49 (dd, J = 8.1, 3.7, 1H, H-3), 4.96 (d, J = 3.7, 1H, H-1), 4.75-4.67 (m, 4H, $-OCH_2OCH_3$ x2), 4.59 (dd, J = 8.1, 1.2, 1H, H-4), 4.19 (app. t, J = 3.7, 1H, H-2), 3.57 (s, 3H, -OMe), 3.33 (2s, 6H, $-OCH_2OCH_3$ x 2), 2.19 (s, 3H, -OAc). **8b** : 1H-nmr ($CDCl_3$): δ 8.1-7.4 (m, 5H, Ar-H), 7.50 (d, J = 2.7, 1H, vinyl-H), 5.68 (dd, J = 3.8, 3.2, 1H, H-3), 4.83-4.64 (m, 4H, $-OCH_2OCH_3$ x2), 4.82 (d, J = 7.8, 1H, H-1), 4.73 (dd, J = 3.8, 2.7, 1H, H-4), 4.15 (dd, J = 7.8, 3.2, 1H, H-2), 3.64 (s, 3H, -OMe), 3.42 & 3.38 (2s, 6H,$-OCH_2OCH_3$ x 2), 2.07 (s, 3H, -OAc). In **8b**, H_{vinyl} showed the nOe relationships with H_1 and H_2.
14. All new compounds have been fully characterized by satisfactory spectral and elemental/HRMS analyses.The stereochemistry of **9** and **2** were determined by extensive ^1H-^1H COSY and difference nOe measurements.
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16. **3** : ^{31}P-nmr (D_2O, pH 10) δ 5.83, 5.08, 4.33; $[\alpha]_D^{26}$ = -19.2 ° (c 1.25, H_2O). **4** : ^{31}P-nmr (D_2O, pH 10) δ 5.83, 5.02 (2P), 4.60; $[\alpha]_D^{25}$ = -33 ° (lithium salt, c 1.00, H_2O; lit.[5b] : free acid, -18.0 °, c 1.2, H_2O).
17. A preliminary study showed that compound **4** had a substantial inhibitory activity of *myo*-inositol $(1,4,5)P_3$ 3-kinase at μM concentrations.

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