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Synthesis of Optically Active Inositol Derivatives Starting from D-Glucurono-6,3-lactone#

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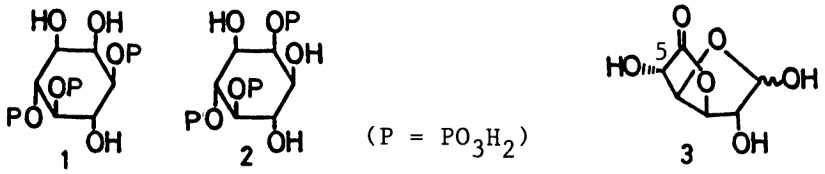
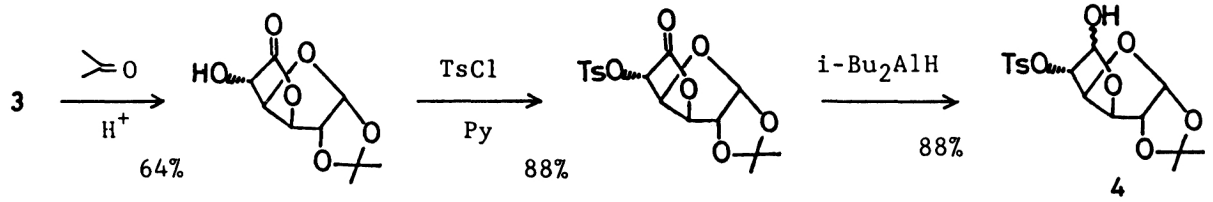
D-Glucurono-6,3-lactone was converted to optically active and partially protected inositols. The synthetic strategy involves an efficient conversion of the D-gluco configuration to the L-ido configuration and reductive cyclization of dials to cyclitols.

Recent biochemical studies have revealed that D-myo-inositol 1,4,5-trisphosphate (1, Ins(1,4,5)P_3) is a cellular second messenger.[1] Its regioisomer Ins(2,4,5)P_3 2 is known to have a similar biological activity.[2] These findings have stimulated biochemical investigation on the matabolic pathway involving inositol phosphates. These phosphates 1 and 2 are obtained by hydrolysis of bovine brain phosphoinositide. However, its isolation and purification are very laborious. Structurally modified inositol phosphates are also necessary to investigate the metabolism and structure-activity relationship. These problems directed us to synthesize various poly-phosphorylated inositol derivatives. In this communication, we describe the



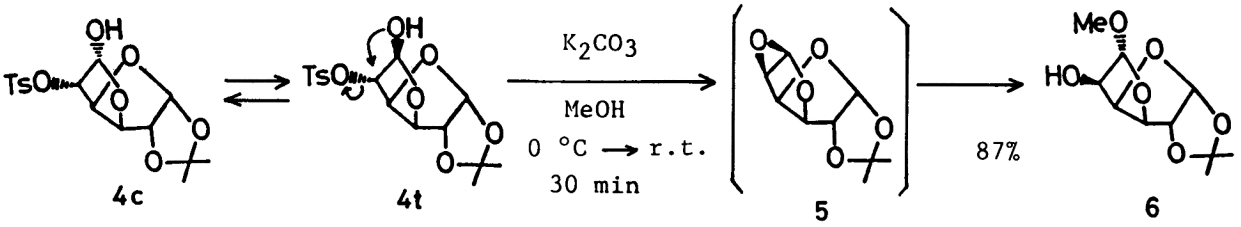
synthesis of partially protected myo-inositols 15 and other stereoisomeric inositols 16 and 17 utilizing D-glucurono-6,3-lactone 3 as an optically active starting material. Among these inositols, 4,5-di-O-allyl-3,6-di-O-benzyl-D-myo-inositol 15b has previously been reported from this laboratory as the key intermediate for the synthesis of 1.[3]

Lactone 3 was converted to an about 1:2 mixture of lactols 4t and 4c according



Scheme 1.

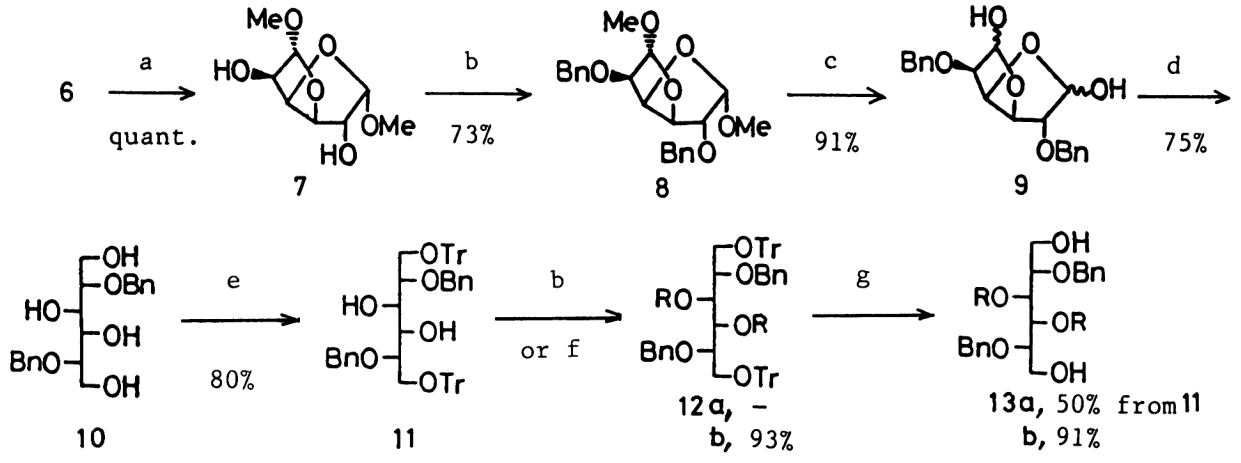
This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 60th birthday.



Scheme 2.

to the literature (Scheme 1).[4] Lactol 4 with the D-gluco configuration is subjected to conversion to an L-ido compound under basic conditions. Since cis isomer 4c is interconvertible with 4t in solution, both isomers can be converted to oxirane 5 which is in turn solvolyzed to ring openig product (Scheme 2). Thus, treatment of 4 with bases such as K_2CO_3, DBU, and t-BuOK in methanol gave the expected methyl glycoside 6.[5] This reaction was affected by reaction temperature and after some experiments, 6 was found to be selectively obtained in high yield when the solution of 4 was cooled by an ice bath during addition of K_2CO_3 and then warmed gradually to room temperature. Smith carried out a mechanistic investigation on a similar epimerization reaction.[6] Weidmann and co-workers reported epimerization at the 5 position of benzoylated 4 under conditions where the reaction was conducted at high temperature for a long reaction time.[4c]

Methanolysis of 6 in the presence of hydrochloric acid afforded stereoselectively 7 in quantitative yield. Two free hydroxyl groups of 7 thus generated were benzylated followed by hydrolysis and reduction to yield 2,5-di-O-benzyl-L-iditol 10[7] (Scheme 3). The stereochemistry of 10 was confirmed by leading it to the corresponding hexaacetate by hydrogenolysis (5% Pd-C, H_2) and subsequent acetylation and by comparing its mp and optical rotation with reported values.[8] After two primary hydroxyl groups of 10 was protected as triphenylmethyl ethers, the resulting ether 11 was benzylated or allylated followed by acid hydrolysis to afford 13. Since dials 14 obtained by Swern oxidation of 13 have a C_2 symmetry axis, exclusive

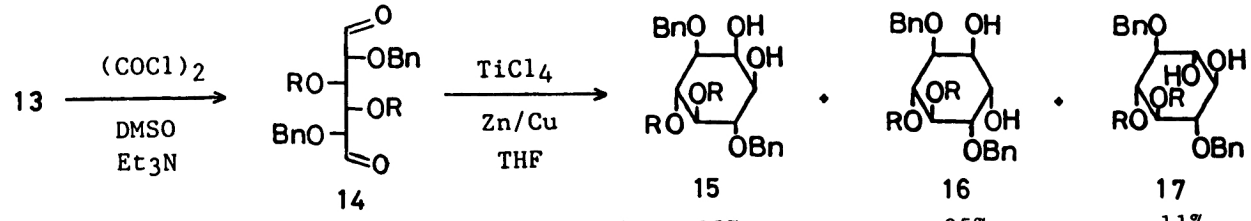


a: R=Bn (benzyl), b: R=All (allyl)

a) HCl/MeOH, b) NaH/BnCl/DMF, c) 2 M-H_2SO_4/AcOH, d) $NaBH_4$/MeOH
e) TrCl/Py, f) NaH/AllBr/DMF, g) 1 M-HCl/Dioxane (1 M=1 mol dm^{-3})

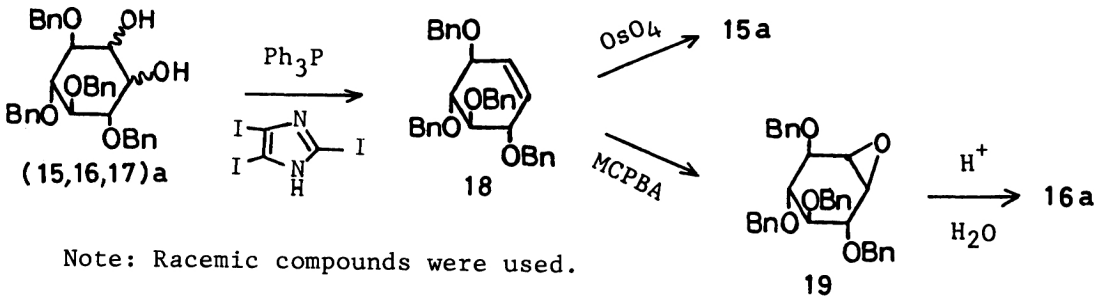
Scheme 3.

formation of myo derivative on treatment of 14 with low valent titanium complexes was expected based on the Corey's observation[9] that hexanedial selectively gave the corresponding cis diol. However, reductive coupling reaction of the present polyoxy dials 14 with low valent titanium species resulted in the formation of two trans diols, chiro- 16[10] and scyllo-inositol 17[11] as well as the expected myo-inositol 15[12] (Scheme 4). Low valent titanium reagents were prepared by the reaction of $TiCl_4$ with various reducing agents such as Zn(Hg), Mg(Hg), and $LiAlH_4$, but all gave similar results. Unusual chiro and scyllo isomers thus easily formed are utilizable for biological investigations.



Scheme 4.

In order to obtain myo isomer exclusively, further transformation of a mixture of reductive cyclization products was examined. Thus, a racemic mixture of 15a, 16a, and 17a (2:2:1) was treated with triphenylphosphine and 2,4,5-triiodoimidazole to afford olefinic product 18 in 73% yield.[13] Since 18 has a C_2 symmetry axis, approach of a reagent from both faces of the double bond yields the same product. Indeed, treatment of 18 with OsO_4 gave 3,4,5,6-tetra-O-benzyl-myo-inositol in 75% yield as a sole product. Similarly, the reaction with MCPBA afforded oxirane 19 which was then transformed to chiro-inositol derivative 16a (trans diaxial product) by acid hydrolysis. However, the ring opening of 19 produced scyllo-inositol as a by-product.[14]



Note: Racemic compounds were used.

Scheme 5.

In conclusion, optically active inositol derivatives were synthesized without optical resolution which is a general method for obtaining optically active inositol derivatives. In this process, we demonstrated a novel method for the transformation of carbohydrate to cyclitol.

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10) 16a: $[\alpha]_D^{18}$+20.0° (c 3.7, $CHCl_3$); IR(nujol) 3420 cm^{-1}; ^1H NMR($CDCl_3$) δ= 4.16 (s, 2H = equatorial protons on C_1 and C_2), 3.83 (s, 4H = axial protons on C_{3-6}). 16b: $[\alpha]_D^{30}$+25.0° (c 1.36, $CHCl_3$); IR(neat) 3420 cm^{-1}; ^1H NMR($CDCl_3$) δ= 4.04 (s, 2H = equatorial protons on C_1 and C_2), 3.80-3.44 (m, 4H = axial protons on C_{3-6}).

11) 17a: mp 144.5-145.0 °C (from hexane-benzene); $[\alpha]_D^{22}$-14.6° (c 1.3, $CHCl_3$); IR (nujol) 3350 cm^{-1}; ^1H NMR($CDCl_3$) δ= 3.68-3.32 (m, 6H = methine protons). 17b: mp 120.0-120.5 °C (from hexane-benzene); $[\alpha]_D^{30}$-12.1° (c 1.32, $CHCl_3$); IR (nujol) 3400 and 3150 cm^{-1}; ^1H NMR($CDCl_3$)δ= 3.51-3.16 (m, 6H = methine protons).

12) 15a: mp 143-143.5 °C (from MeOH); $[\alpha]_D^{18}$-18.6° (c 1.4, $CHCl_3$). [lit: mp 141-143 °C; $[\alpha]_D^{20}$-24.3° (c 1.3, $CHCl_3$).]: V. I. Shvets, B. A. Klyashchitskii, S. E. Stepanov, and R. P. Evstigneeva, Tetrahedron, 29, 331 (1973). 15b: mp 106-107 °C (from benzene-hexane); $[\alpha]_D^{30}$-12.6° (c 0.59, $CHCl_3$). This compound was characterized by comparison of its physical and spectroscopic data with those of 15b obtained in Ref. 3.

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14) Transformation of 18 to 16a is unsatisfactory with respect to yield at the present time.

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