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FACILE ASYMMETRIC SYNTHESIS OF THE D-*MYO*-INOSITOL DERIVATIVE FROM DIETHYL 2,3-*O*-ISOPROPYLIDENE-D-TARTRATE

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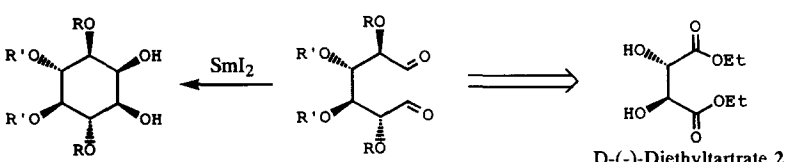
Abstract: A facile asymmetric synthesis of the D-*myo*-inositol derivative was achieved from diethyl 2,3-*O*-isopropylidene-D-tartrate in 7 steps. The two carboxylate groups of diethyl tartrate were converted simultaneously into dialdehyde to afford a key intermediate (**1**) for the synthesis of various protected D-*myo*-inositols.

Polyphosphoinositides play significant roles in the cellular signal transduction systems[1]. Phosphatidyl-D-*myo*-inositol 4,5-bisphosphate is hydrolyzed by phospholipase C, which is activated on stimulation with many growth factors, to give diacylglycerol and D-*myo*-inositol 1,4,5-trisphosphate. Then diacylglycerol activates protein kinase C and D-*myo*-inositol 1,4,5-trisphosphate promotes release of intracellular Ca^{2+}. In addition, PI-3 kinase phosphorylates phosphatidyl-D-*myo*-inositol 4,5-bisphosphate to phosphatidyl-D-*myo*-inositol 3,4,5-trisphosphate, which may act as a second messenger in cellular signal transduction[2].

Since the supply of polyphosphoinositides from natural sources is very limited, extensive efforts have been made to synthesize racemic and homochiral inositol derivatives[1]. Recently we synthesized 1-*O*-alkyl- and 1-*O*-acyl-D-*myo*-inositol 3,4,5-trisphosphates as new analogues of phosphatidyl-D-*myo*-inositol 3,4,5-trisphosphate[3]. Here we describe a highly efficient asymmetric synthesis of enantiomerically pure inositol derivatives from diethyltartrate.

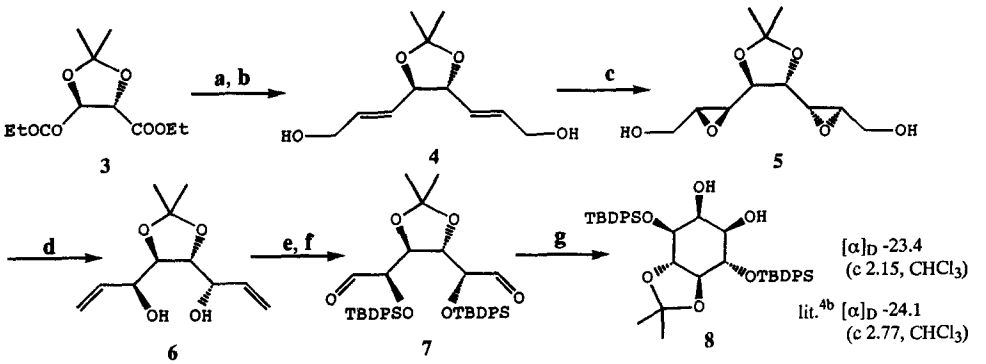
In 1987, Ozaki and co-workers[4a] reported the synthesis of D-*myo*-inositol derivatives through intramolecular pinacol coupling mediated by low-valent titanium reagent. In 1994, Chiara et al.[4b] and Mioskowski et al.[4c] independently reported an elegant stereoselective synthesis of inositol derivatives via pinacol coupling of dialdehyde (**1**) using samarium diiodide. However, preparation of **1** requires multistep reactions from D-mannitol[4b] or L-sorbose[4c]. We planned to synthesize **1** from readily available diethyl 2,3-*O*-isopropylidene-D-tartrate in a stereo-controlled manner (**Scheme 1**).

Scheme 1



Dialdehyde **1** D-(-)-Diethyltartrate **2**

Scheme 2



3 4 5 6 7 8

Reagents and conditions : a. DIBALH, toluene, -78°C, 2 h, then sodium trimethylphosphonoacetate, DME, -78°C to r.t., 12 h, 74%; b. DIBALH, CH_2Cl_2, -78°C to 0°C, 1 h, 78%; c. $Ti(OiPr)_4$, D-(-)-diethyltartrate, cumene hydroperoxide, MS-4A, CH_2Cl_2, -20°C, 2 days, 73%; d. triphenylphosphine, imidazole, iodine, THF, 0°C, 5 min, then, NH_4Cl, Zn, EtOH, r.t., 30 min, 97%; e. *t*-butylchlorodiphenylsilane, imidazole, DMF, 0°C to r.t., 18 h, 99%; f. O_3, MeOH, -78°C, 20 min, then dimethylsulfide, -78°C to r.t., 30 min, 94%; g. samarium diiodide, *t*-BuOH, THF, -78°C to r.t., 18 h, 87%

DIBALH reduction of diethyl-2,3-*O*-isopropylidene-D-tartrate (**3**) followed by Wittig-Horner reaction in one pot afforded an (*E,E*)-diester (*EE* : *EZ* = 10 : 1)[5], which was reduced with DIBALH to give the (*E,E*)-bisallyl alcohol (**4**)[6]. Sharpless asymmetric epoxidation of **4** proceeded diastereoselectively to give the bisepoxy alcohol **5**[7] as the sole product. Substitution of the hydroxy groups in **5** with iodine and successive reduction with Zn[8] gave **6**[9] in 97% yield. The protection of both hydroxy groups with *t*-butylchlorodiphenylsilane and ozonolysis of olefins, followed by reductive workup, gave the known dialdehyde **7**[4b], which was transformed to 3,6-di-*O*-*t*-butyldiphenylsilyl-4,5-*O*-isopropylidene-D-*myo*-inositol (**8**) according to the reported procedure[4b]. The overall yield of **8** from **3** through 7 steps was 33 %.

Our current synthetic method should provide easy access to a variety of chiral polyphosphoinositides and other *myo*-inositol polyphosphate derivatives.

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(7) ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41 (s, 6H), 2.37 (br, 2H), 3.15 (brm, 2H), 3.22 (m, 2H), 3.76 (dd, *J* 3.5, 13.0 Hz, 2H), 3.87 (dd, *J* 3.0 and 13.0 Hz, 2H), 3.90 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.6, 54.3, 55.3, 60.9, 77.3, 110.8. $[\alpha]_D$ +33.8 (c=1.07, $CHCl_3$).

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(9) ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (s, 6H), 2.29 (d, *J* 7 Hz, 2H), 4.01 (dd, *J* 1.5, 3.0 Hz, 2H), 4.14 (m, 2H), 5.27 (td, *J* 1.5, 10.5 Hz, 2H), 5.38 (td, *J* 1.5, 17.5 Hz, 2H), 5.89 (ddd, *J* 6.0, 10.5, 17.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.1, 71.8, 79.3, 109.6, 116.9, 136.7. $[\alpha]_D$ -3.05 (c=1.44, $CHCl_3$).

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