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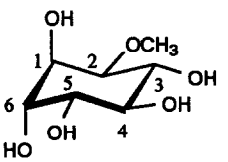
CHIRAL SYNTHESIS OF D-*MYO*-INOSITOL 1-PHOSPHATE STARTING FROM L-QUEBRACHITOL

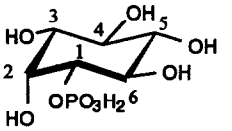
Takahiko Akiyama, Naoto Takechi, and Shoichiro Ozaki*
Department of Resources of Chemistry, Faculty of Engineering,
Ehime University, Bunkyo-cho, Matsuyama 790, Japan

Summary: D-*Myo*-inositol 1-phosphate was synthesized from L-quebrachitol *via* stereoselective inversion of a 3-hydroxyl group and chemoselective demethylation.

Recently, inositol phosphates have stimulated considerable attention from the standpoint of its biosynthesis, function, and metabolism since the discovery that D-*myo*-inositol 1,4,5-triphosphate (Ins(1,4,5)P_3) acts as the probable intracelluar second messenger for calcium mobilization.[1] A number of synthetic procedures for inositol phosphates have appeared so far.[2] A drawback of these syntheses is that tedious optical resolution is necessary in synthesizing chiral inositol phosphates. To develop a practical synthesis of biologically active D-*myo*-inositol phosphates, we focused on L-quebrachitol (L-2-*O*-methyl-*chiro*-inositol),[3] obtained from an exudate of the rubber tree as a starting material. Two problems must be circumvented; stereospecific inversion of 1-OH group and demethylation of 2-OCH_3 group. Although chiral syntheses of L-*myo*-inositol 1-phosphate[4] and L-*myo*-inositol 1,4,5-triphosphate[5] from L-quebrachitol have appeared, no effective transformation of L-quebrachitol into biologically active D-*myo*-inositol phosphate[6] has been reported.



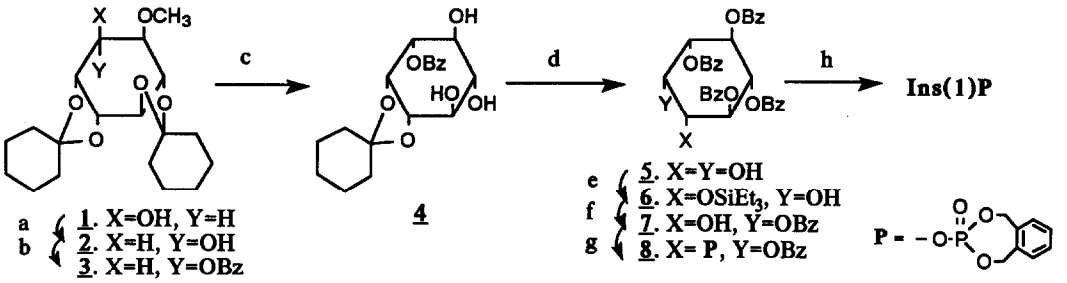
L-Quebrachitol



Ins(1)P

Oxidation of 1L-3,4;5,6-Dicyclohexylidene-2-*O*-methyl-*chiro*-inositol (1)[4], followed by $LiBH_4$ effected highly stereoselective reduction to the inverted alcohol **2**. Crucial demethylation was attempted by treatment of **3**, obtained through a conventional benzoylation of **2**, with HI or BCl_3,[4,7,8] but both benzoyl and cyclohexylidene groups were affected under these reaction conditions. We found NaI-$AlCl_3$ system[9] was effective in demethylation of the benzoate **3**. Treatment of **3** in CH_3CN in the presence of $AlCl_3$ (10 eq) and NaI (10 eq) at room temperature overnight furnished a triol **4**[10] as a crystal in 83% yield. It is noteworthy that both methyl ether and *trans* cyclohexylidene group were cleaved in preference to the *cis* cyclohexylidene moiety.

Perbenzoylation of **4**, followed by acid hydrolysis gave a diol **5**, which was allowed to react with triethylsilyl chloride in pyridine to give exclusively a 1-silylated alcohol **6**. Subsequent benzoylation and desilylation afforded an alcohol **7** in 93% yield from **5**. Phosphorylation was carried out according to the newly developed procedure[11] to give **8**. Deprotection of phosphate group followed by debenzoylation gave D-*myo*-



Reagents and conditions: a. i)Ac_2O, DMSO, CH_2Cl_2, reflux 8hr, 100%, ii)$LiBH_4$, THF, -78°C, 20min, 92 %. b. PhCOCl, NEt_3, DMAP, CH_2Cl_2, 0°C, 88%. c. $AlCl_3$-NaI, CH_3CN, r.t. overnight, 83 %. d. i)PhCOCl, NEt_3, DMAP, CH_2Cl_2 99%. ii)CF_3COOH, MeOH, r.t. 96 %. e. Et_3SiCl, Py, 0 °C, 100 %, f. i)PhCOCl, NEt_3, DMAP, CH_2Cl_2, 93 %. ii)p-TsOH, 80 % AcOH, 100%. g. i)1H-Tetrazole, 3-diethylamino-1,5-dihydro-2,4,3-benzodioxaphosphepine, CH_2Cl_2, ii)H_2O, iii)m-CPBA, 93%. h. i)10% Pd/C, H_2, MeOH. ii)NaOMe, MeOH, r.t. 81%

inositol 1-phosphate (Ins(1)P) which was isolated as its crystalline biscyclohexylamine salt in 81% yield. Chiral inositol 1-phosphate prepared in this way has been shown to contain no detectable inositol 2-phosphate by 270MHz ^{1}H-NMR. Ins(1)P was obtained totally 37% from L-quebrachitol. This newly developed process is very efficient since; 1) excellent yields of all reactions make purification of products very easy; 2) optical resolution process is not necessary.

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10. 4; ^{1}H-NMR (270MHz,$CDCl_3$, δ) 1.25-1.75 (10H, m), 2.60-3.20 (3H, m), 3.36 (1H, dd, H5, J_{54}=10Hz, J_{56}=11Hz), 3.37 (1H, dd, H6, J_{61}=8Hz, J_{65}=11Hz), 3.98 (1H, t, H4, J_{43}=J_{45}=10Hz), 4.09 (1H, dd, H1, J_{16}=8Hz, J_{12}=6Hz), 4.53(1H, t, H2, J_{21}=J_{23}=6Hz), 5.23 (1H, dd, J_{32}=6Hz, J_{34}=10Hz), 7.40-7.65 (3H, m), 8.05-8.20 (2H,m). $[\alpha]_D^{22}$ = +53.3 ° (c 1.22, EtOH), m.p. 198-200 °C
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