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SYNTHESES OF TWO ENANTIOMERIC PAIRS OF *MYO*-INOSITOL(1,2,4,5,6) AND -(1,2,3,4,5) PENTAKISPHOSPHATE

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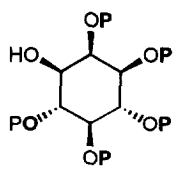
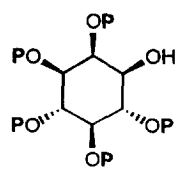
Abstract: Two enantiomeric pairs of *myo*-inositol(1,2,4,5,6)P_5 and -(1,2,3,4,5)P_5 have efficiently been synthesized by means of the lipase catalyzed acetylation of 1,2:5,6-di-*O*-isopropylidene-*myo*-inositol and the benzoyl migration procedure.

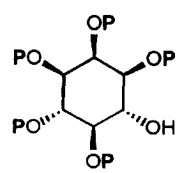
Since the discovery that D-*myo*-inositol-1,4,5-trisphosphate [Ins(1,4,5)P_3] plays a pivotal role as a second messenger in the transmembrane signaling, thus mobilizing calcium ions from the intracellular storage, its interaction with the I(1,4,5)P_3 receptor and metabolic enzymes has been a subject of intensive investigations.[1] One of the major metabolic pathways involves a specific phosphorylation of Ins(1,4,5)P_3 to Ins(1,3,4,5)P_4 by Ins(1,4,5)P_3-3-kinase.[2] Although IP_5s were not recognized as naturally occurring metabolites of IP_3 and IP_4 until recently, their biological roles and functional importances have been implicated in many biological systems.[3] In addition, some of the synthetic IP_5 regioisomers such as D/L-Ins(1,2,3,4,5)P_5 (**2**) were found to show high affinities toward the D-Ins(1,3,4,5)P_4 receptor protein purified from pig cerebellum.[4] There exist six possible IP_5 regioisomers: two *meso* compounds [Ins(1,3,4,5,6)P_5, Ins(1,2,3,4,6)P_5] and two pairs of enantiomers [D/L-Ins(1,2,4,5,6)P_5, D/L-Ins((1,2,3,4,5)P_5]. Several groups have reported syntheses of *meso* and racemic IP_5 isomers,[5] including the synthesis of all possible regioisomers of IP_5 based on the benzoyl group migration method.[6] Very recently, the first synthesis of chiral IP_5s via the camphanate ester resolution route was reported.[7] We wish to report herein our efforts on the synthesis of the two enantiomeric pairs of Ins(1,2,4,5,6)P_5 (**1**) and Ins(1,2,3,4,5)P_5 (**2**)



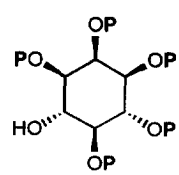
1D



1L



2D



2L

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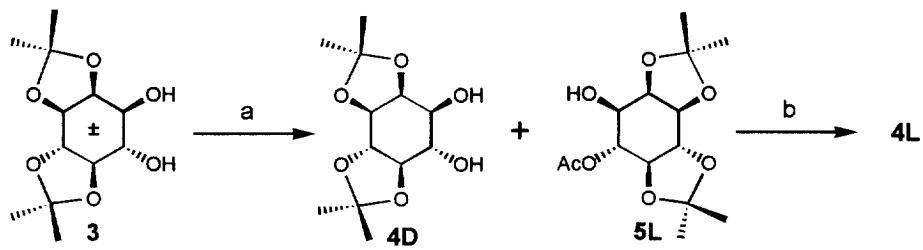
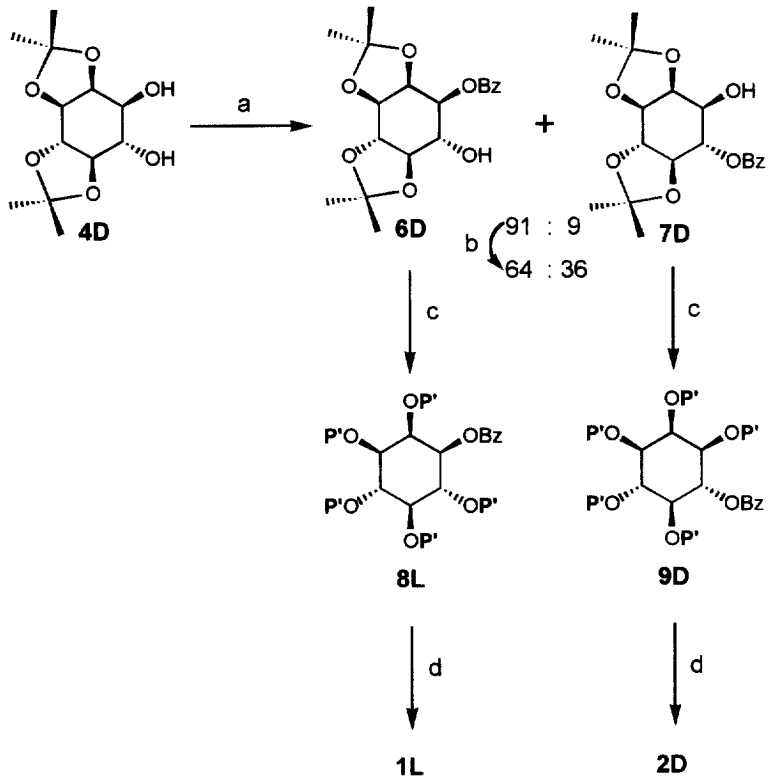
Our synthetic approaches to homochiral **1** and **2** are based on the enzyme catalyzed asymmetric acetylation of 1,2:5,6-di-*O*-isopropylidene-*myo*-inositol (**3**). Thus, racemic diol **3**[8] in diethyl ether was subjected to acetic anhydride in the presence of lipase from *Candida rugosa* (Sigma, CRL). The reaction was stopped at ca. 50% completion, and the product was filtered through celite and chromatographed on silica gel to give the unreacted diol (**4D**, 46%, 87% ee) and the monoacetylated product (**5L**, 48%, 84% ee). Hydrolysis of **5L** with LiOH in aqueous methanol gave **4L** in good yield. The optical purities of **4D** and **4L** could be improved to 98% ee upon recrystallization from hexane and $CHCl_3$ (1:1) in ca. 70% recovery.[9] The absolute configurations of **4D** and **4L** were determined on the basis of the HPLC retention time on a Chiralcel OD column, after their conversion to the I(1,4,5,6)Bz_4 derivatives.[10] Thus, benzoylation of **4D** with excess BzCl in pyridine, followed by a) acid-catalyzed partial solvolysis (p-TsOH, MeOH-CH_2Cl_2) of the *trans*-acetal of **4D**-Bz_2, b) further benzoylation, and c) acid-catalyzed removal of the *cis*-acetal gave D-I(1,4,5,6)Bz_4. Similarly, **4L** was converted to L-I(1,4,5,6)Bz_4. The retention time of D-I(1,4,5,6)Bz_4 was found to be 6.64 min while that of L-I(1,4,5,6)Bz_4 was 9.82 (Chiralcel OD column, iPrOH-heptane 1:3, flow rate 2.0 ml/min), in accord with the reported order of retention times.[10]



Scheme 1. a. CRL, Ac_2O/Et_2O, RT. b. LiOH, H_2O-MeOH, 0 °C.

Chiral diol **4D** was monobenzoylated under the conventional conditions employing BzCl in pyridine to give a mixture of **6D** and **7D** (in 91:9 ratio based on ^{1}H-NMR, 82% yield). The base-catalyzed benzoyl migration[11] of the crude product shifted the ratio to **6D** : **7D** = 64:36.[12] After column chromatography, **6D** and **7D** each was hydrolyzed in hot aqueous acetic acid, and the product was phosphorylated by successive reactions with diethyl chlorophosphite and diisopropylethylamine in DMF, and then 30% H_2O_2 to afford **8L** and **9D**.[13] In the final step, all protecting groups were removed by successive treatments with TMSBr and then LiOH. The sodium salt of the target compounds **1L** and **2D** were obtained after ion exchange chromatography on Dowex 50x8-100 (H^+ form), pH adjustment to 10 with NaOH, and lyophilization (Scheme 2).[14] Compound **4L** was analogously transformed to **1D** and **2L**.[14]



Scheme 2. a. BzCl, pyridine, 82% (sum of **6D** and **7D**). b. pyridine-H_2O (6:4), 100 °C, 1h. c. (i) 80% aq. AcOH, 100 °C, 1h. (ii) $(EtO)_2P$-Cl, iPr_2NEt, DMF. (iii) H_2O_2, ~50%. d. (i) TMSBr, CH_2Cl_2. (ii) 1N LiOH, 80 °C, 3h. (iii) H^+ ion-exchange. (iv) NaOH, pH 10, quant.

In sum, we have successfully prepared each enantiomer of I(1,2,4,5,6)P_5 (**1D** and **1L**) and I(1,2,3,4,5)P_5 (**2D** and **2L**) via the CRL catalyzed asymmetric acetylation of 1,2:5,6-di-*O*-isopropylidene-*myo*-inositol and the benzoyl migration procedure.

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References and Notes

* Dedicated to Professor Robert M. Coates (University of Illinois) on the occasion of his 60th Birthday.

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9. The CRL catalyzed acetylation could routinely be run in 5-10 g scales. **4D**: mp 151-153 °C, $[\alpha]_D^{27}$ +9.12 (c 0.74, $CHCl_3$); **4L**: mp 151-153 °C, $[\alpha]_D^{28}$ -8.85 (c 1.0, $CHCl_3$). A similar but smaller scale resolution of 1,2:5,6-dicyclohexylidene-*myo*-inositol with bovine pancreas cholesterol esterase was previously reported: Liu, Y.-C.; Chen, C.-S. *Tetrahedron Lett.* **1989**, *30*, 1617-1620.
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12. R_f values for **6D** and **7D** are 0.2 and 0.25 (ethyl acetate : n-hexane = 1 : 2). **6D**: mp 183-186 °C, $[\alpha]_D^{27}$ -24.4 (c 0.53, CH_3OH); **7D**: mp 139-142 °C, $[\alpha]_D^{27}$ +6.9 (c 0.62, CH_3OH); **6L**: mp 184-186 °C, $[\alpha]_D^{27}$ +23.8 (c 0.63, CH_3OH); **7L**: mp 142-143 °C, $[\alpha]_D^{27}$ -6.3 (c 0.69, CH_3OH).
13. **8L**: $[\alpha]_D^{27}$ -12.5 (c 0.62, CH_2Cl_2); **9D**: $[\alpha]_D^{27}$ +6.0 (c 0.60, CH_2Cl_2); **8D**: $[\alpha]_D^{27}$ +13.7 (c 1.58, CH_2Cl_2); **9L**: $[\alpha]_D^{27}$ - 4.6 (c 1.43, CH_2Cl_2).
14. **1D**: $[\alpha]_D^{25}$ -6.0 (c 0.40, H_2O, *pH* 10), lit. $[\alpha]_D^{24}$ -7.1 (c 0.83, H_2O, *pH* 1.6)[7]; **1L**: $[\alpha]_D^{25}$ +7.5 (c 0.40, H_2O, *pH* 9.5), lit. $[\alpha]_D^{24}$ -6.2 (c 0.96, H_2O, *pH* 1.6)[7]; **2D**: $[\alpha]_D^{25}$ -5.0 (c 0.40, H_2O, *pH* 9.2), lit. $[\alpha]_D^{24}$ -4.0 (c 0.23, H_2O, *pH* 1.6)[7]; **2L**: $[\alpha]_D^{25}$ +5.8 (c 0.40, H_2O, *pH* 9.5), lit. $[\alpha]_D^{24}$ +4.3 (c 0.43, H_2O, *pH* 1.6)[7].