

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

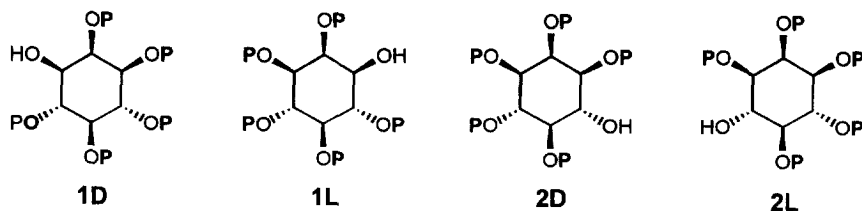
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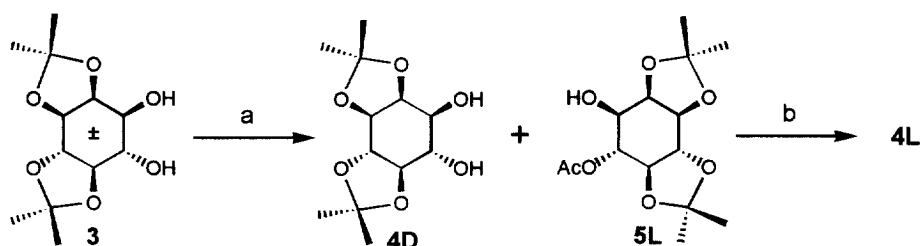
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**Abstract:** Two enantiomeric pairs of *myo*-inositol(1,2,4,5,6) $P_5$  and -(1,2,3,4,5) $P_5$  have efficiently been synthesized by means of the lipase catalyzed acetylation of 1,2:5,6-di-*O*-isopropylidene-*myo*-inositol and the benzoyl migration procedure. © 1998 Elsevier Science Ltd. All rights reserved.

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.<sup>1</sup> 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.<sup>2</sup> Although IP<sub>5</sub>s were not recognized as naturally occurring metabolites of IP<sub>3</sub> and IP<sub>4</sub> until recently, their biological roles and functional importances have been implicated in many biological systems.<sup>3</sup> In addition, some of the synthetic IP<sub>5</sub> 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.<sup>4</sup> There exist six possible IP<sub>5</sub> 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<sub>5</sub> isomers,<sup>5</sup> including the synthesis of all possible regioisomers of IP<sub>5</sub> based on the benzoyl group migration method.<sup>6</sup> Very recently, the first synthesis of chiral IP<sub>5</sub>s via the camphanate ester resolution route was reported.<sup>7</sup> 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)

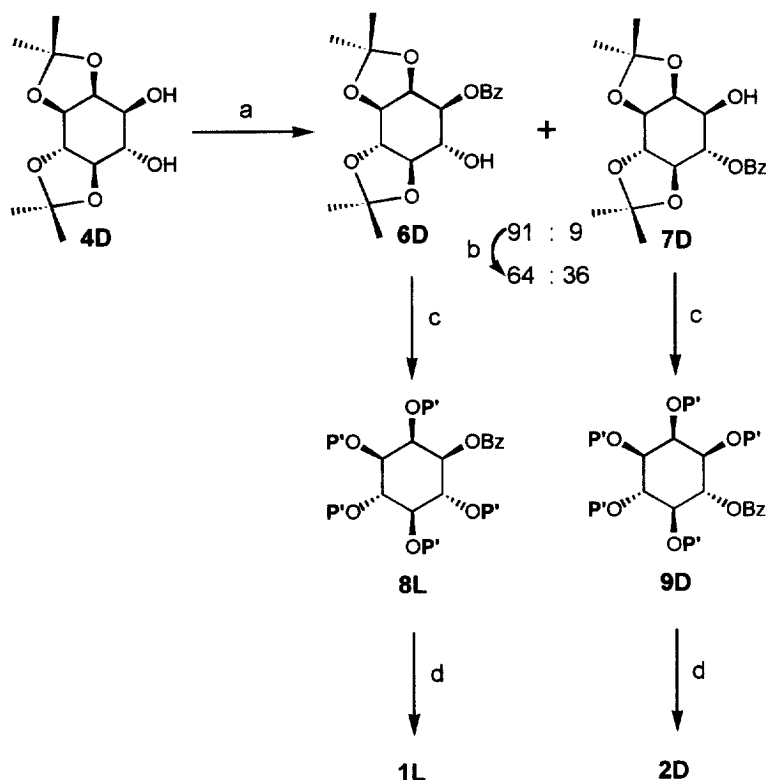


Our synthetic approaches to homochiral **1** and **2** are based on the enzyme catalyzed asymmetric acetylation of 1,2:5,6-di-*O*-isopropylidene-*myo*-inositol (**3**). Thus, racemic diol **3**<sup>8</sup> in diethyl ether was subjected to acetic anhydride in the presence of lipase from *Candida rugosa* (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<sub>3</sub> (1:1) in ca. 70% recovery.<sup>9</sup> 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<sub>4</sub> derivatives.<sup>10</sup> Thus, benzylation of **4D** with excess BzCl in pyridine, followed by a) acid-catalyzed partial solvolysis (p-TsOH, MeOH-CH<sub>2</sub>Cl<sub>2</sub>) of the *trans*-acetal of **4D**-Bz<sub>2</sub>, b) further benzylation, and c) acid-catalyzed removal of the *cis*-acetal gave D-I(1,4,5,6)Bz<sub>4</sub>. Similarly, **4L** was converted to L-I(1,4,5,6)Bz<sub>4</sub>. The retention time of D-I(1,4,5,6)Bz<sub>4</sub> was found to be 6.64 min while that of L-I(1,4,5,6)Bz<sub>4</sub> 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.<sup>10</sup>



Scheme 1. a. CRL, Ac<sub>2</sub>O/Et<sub>2</sub>O, RT. b. LiOH, H<sub>2</sub>O-MeOH, 0 °C.

Chiral diol **4D** was monobenzyolated under the conventional conditions employing BzCl in pyridine to give a mixture of **6D** and **7D** (in 91:9 ratio based on <sup>1</sup>H-NMR, 82% yield). The base-catalyzed benzoyl migration<sup>11</sup> of the crude product shifted the ratio to **6D** : **7D** = 64:36.<sup>12</sup> 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<sub>2</sub>O<sub>2</sub> to afford **8L** and **9D**.<sup>13</sup> 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<sup>+</sup> form), pH adjustment to 10 with NaOH, and lyophilization (Scheme 2).<sup>14</sup> Compound **4L** was analogously transformed to **1D** and **2L**.<sup>14</sup>



Scheme 2. a. BzCl, pyridine, 82% (sum of **6D** and **7D**). b. pyridine-H<sub>2</sub>O (6:4), 100 °C, 1h. c. (i) 80% aq. AcOH, 100 °C, 1h. (ii) (EtO)<sub>2</sub>P-Cl, iPr<sub>2</sub>NEt, DMF. (iii) H<sub>2</sub>O<sub>2</sub>, ~50%. d. (i) TMSBr, CH<sub>2</sub>Cl<sub>2</sub>. (ii) 1N LiOH, 80 °C, 3h. (iii) H<sup>+</sup> ion-exchange. (iv) NaOH, pH 10, quant.

In sum, we have successfully prepared each enantiomer of I(1,2,4,5,6)P<sub>5</sub> (**1D** and **1L**) and I(1,2,3,4,5)P<sub>5</sub> (**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<sub>3</sub>); **4L**: mp 151-153 °C,  $[\alpha]_D^{28} -8.85$  (c 1.0, CHCl<sub>3</sub>). 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<sub>f</sub>* 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<sub>3</sub>OH); **7D**: mp 139-142 °C,  $[\alpha]_D^{27} +6.9$  (c 0.62, CH<sub>3</sub>OH); **6L**: mp 184-186 °C,  $[\alpha]_D^{27} +23.8$  (c 0.63, CH<sub>3</sub>OH); **7L**: mp 142-143 °C,  $[\alpha]_D^{27} -6.3$  (c 0.69, CH<sub>3</sub>OH).
13. **8L**:  $[\alpha]_D^{27} -12.5$  (c 0.62, CH<sub>2</sub>Cl<sub>2</sub>); **9D**:  $[\alpha]_D^{27} +6.0$  (c 0.60, CH<sub>2</sub>Cl<sub>2</sub>); **8D**:  $[\alpha]_D^{27} +13.7$  (c 1.58, CH<sub>2</sub>Cl<sub>2</sub>); **9L**:  $[\alpha]_D^{27} -4.6$  (c 1.43, CH<sub>2</sub>Cl<sub>2</sub>).
14. **1D**:  $[\alpha]_D^{25} -6.0$  (c 0.40, H<sub>2</sub>O, pH 10), lit.  $[\alpha]_D^{24} -7.1$  (c 0.83, H<sub>2</sub>O, pH 1.6)<sup>7</sup>; **1L**:  $[\alpha]_D^{25} +7.5$  (c 0.40, H<sub>2</sub>O, pH 9.5), lit.  $[\alpha]_D^{24} -6.2$  (c 0.96, H<sub>2</sub>O, pH 1.6)<sup>7</sup>; **2D**:  $[\alpha]_D^{25} -5.0$  (c 0.40, H<sub>2</sub>O, pH 9.2), lit.  $[\alpha]_D^{24} -4.0$  (c 0.23, H<sub>2</sub>O, pH 1.6)<sup>7</sup>; **2L**:  $[\alpha]_D^{25} +5.8$  (c 0.40, H<sub>2</sub>O, pH 9.5), lit.  $[\alpha]_D^{24} +4.3$  (c 0.43, H<sub>2</sub>O, pH 1.6)<sup>7</sup>.