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The Regioselective Synthesis of Enantiomerically Pure myo-Inositol Derivatives. Efficient Synthesis of myo-Inositol 1,4,5-trisphosphate.

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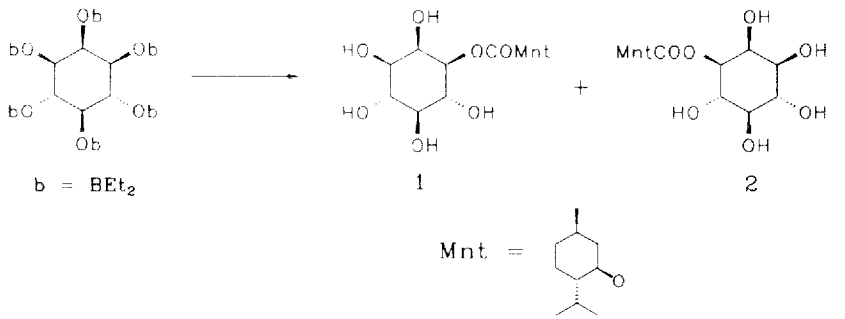
Abstract : Regioselective 1-*O*-acylation of *myo*-inositol and simultaneous optical resolution has been achieved by perborylation, transmetallation using di-*n*-butyltin-bis-acetylacetonate and then acylation with (-)-menthyl chloroformate. Diastereomerically pure 1-*O*-(-)-menthoxycarbonyl-*myo*-inositol **1** can be used as starting material for the preparation of biologically important *myo*-inositol phosphates and glycosyl phosphatidylinositols in a shorter and effective way.

The biological importance of inositol phosphates[1] and glycosyl phosphatidyl inositols[2] has brought about the development of new synthetic strategies for the preparation of enantiomerically pure *myo*-inositol derivatives. Starting from *myo*-inositol the main synthetic problems are related to the regioselectivity of the transformations on a compound with six hydroxyl groups of similar reactivity and the resolution of racemates formed because of its symmetry properties. Useful syntheses of optically active *myo*-inositol phosphates have been reported which use *myo*-inositol *bis*-acetals or *myo*-inositol orthoformate as starting materials[3]. Recently practical syntheses of *myo*-inositol 1,4,5-trisphosphate (IP_3) using enzymatic resolution of racemates[4] or an enantioselective acylation of 1,3,5-tri-*O*-benzyl-*myo*-inositol[5] have been reported. We now report on a new synthetic strategy that starting from *myo*-inositol deals simultaneously with both regio and stereoselectivity problems and allows the preparation of optically active *myo*-inositol derivatives in a shorter and effective way. Using this general strategy the necessary precursors and intermediates for the synthesis of *myo*-inositol phosphates and glycosyl phosphatidyl inositols can be readily prepared in a good yield.

We have recently used a modification of the transmetallation reaction of borylated carbohydrates with tri-n-butyltin acetylacetonate[6] ($Bu_3Snacac$) for the regioselective alkylation and acylation of *myo*-inositol with good results[7]. Using di-n-butyltin-bis-acetylacetonate[8] ($Bu_2Sn(acac)_2$), instead of $Bu_3Snacac$, 1-*O*-alkylated and 1-*O*-acylated derivatives have now been obtained in high yield and excellent regioselectivity (70-80 %). When the regioselective acylation was carried out with a chiral electrophile a pair of diastereomeric 1-*O*-acylderivatives could be obtained and the regioselectively substitued diastereomeric mixture could be resolved at this stage (Scheme I). Thus, *myo*-inositol (8 g) was borylated[9] and transmetallated with $Bu_2Sn(acac)_2$ (1.1 equiv.). The di-n-butyltin intermediate was treated with (-)-menthyl chloroformate (1.3 equiv.) and N-methylimidazol (0.5 equiv.) in toluene at -30 °C. The reaction mixture

was allowed to reach room temperature (25 °C) and left for 20 h. After evaporation of the solvent and treatment with methanol a 2:1 (g.l.c., 70 %) mixture of the diastereomers **1** and **2** was obtained. By washing with hexane/acetone (5/1, v:v) the oily residue was converted into a white solid which was disolved in EtOH and filtered off to separate the unreacted *myo*-inositol (20 % g.l.c.). Evaporation and recrystallization of the residue in ethyl acetate/ethanol (2/1, v:v) gave optically pure 1-*O*-menthoxycarbonyl *myo*-inositol **1** [30 %, $[\alpha]_D$ -71° (*c* 1.5, MeOH), mp 171-173 °C].

Scheme I



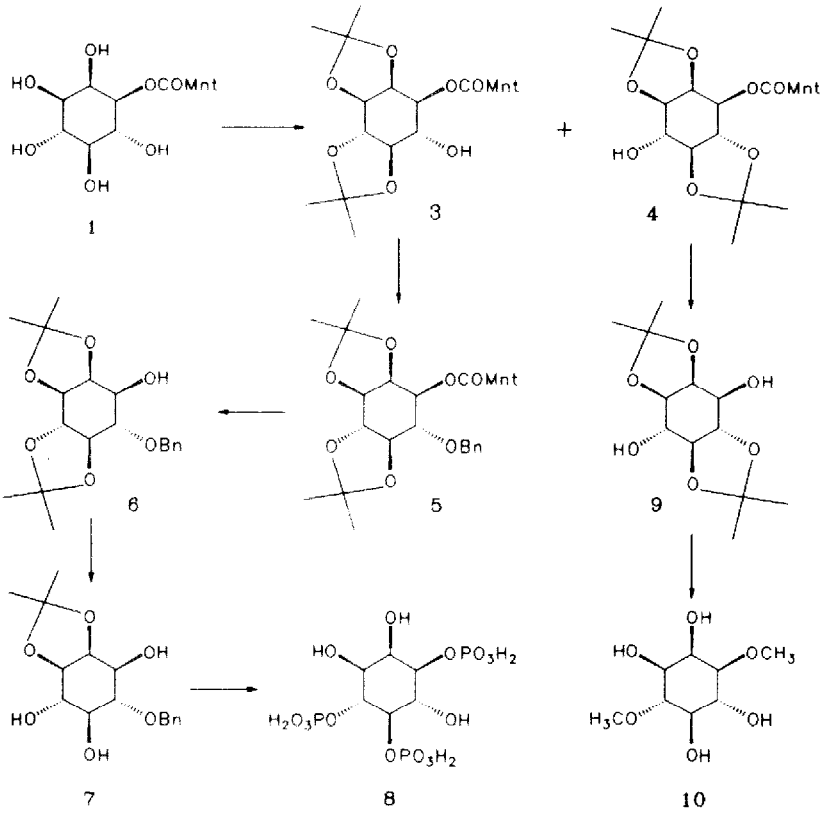
By addition of hexane to the mother liquors a solid was obtained that after recrystallization as above gave 3-*O*-menthoxycarbonyl *myo*-inositol **2** [20 %, $[\alpha]_D$ -16 (*c* 1.7, MeOH), mp 183-186 °C]. The diastereomeric purity of each compound exceeded 98 % as determined both by g.l.c. and ^{1}H-NMR. The absolute configuration of **1** was determined after transformation into the natural D-(-)-liriodendritol[10] (**10**) [a) 2,2-dimethoxypropane, p-TsOH; b) NaOMe/MeOH, **9**[13], 97%; c) MeI/NaH, DMF; d) AcOH 50%; $[\alpha]_D$ -25° (*c* 1.5, H_2O), mp 221-222 °C; Lit.[10] $[\alpha]_D$ -25, mp 224 °C].Compounds **1** and **2** are valuable starting materials for the synthesis of both enantiomers of a variety of *myo*-inositol derivatives. As an example the synthesis of IP_3 will now be described.

For the synthesis of IP_3, compound **1** was acetalated with 2,2-dimethoxypropane in the presence of pTsOH at 25 °C to afford, after chromatography (silica gel, hexane/EtOAc,2/1), the bis-acetals **3** [51 %, $[\alpha]_D$ -61° (*c* 1.0, MeOH), mp 62-64 °C] and **4** [40 %, $[\alpha]_D$ -64° (*c* 0.73, MeOH), mp 184-186 °C] (Scheme II). Benzylation of **3** with benzyl bromide in the presence of Ag_2O gave **5** [91 %, $[\alpha]_D$ -47° (*c* 0.9, $CHCl_3$), mp 60-65 °C]. Treatment of **5** with NaOMe/MeOH gave **6** [90 %, $[\alpha]_D$ -16° (*c* 0.9, $CHCl_3$), mp 89-91 °C], which, on the other hand, is an obvious synthon for the preparation of *myo*-inositol 1-phosphate. Selective removal, using pyridinium p-toluensulphonate, of the 4,5-*O*-isopropylidene group gave triol **7** [85 %, $[\alpha]_D$ + 12° (*c* 0.6, MeOH), mp 120-121 °C]. Phosphitylation of **7** with *N*,*N*-diisopropyldibenzyl phosphoramidite[11] (3 equiv.) in the presence of 1-*H*-tetrazol (5 equiv.) followed by oxidation and then full deprotection (H_2/Pd-C, EtOH) afforded *myo*-inositol 1,4,5-tris(phosphate) **8**, isolated as cyclohexylamonium salt [75 % three steps, $[\alpha]_{546}$ -17° (pH 7, *c* 1.1, H_2O, calculated for the free acid), $[\alpha]_{546}$ -46° (pH 12, *c* 1.0,

H_2O/cyclohexylamine 10/1, calculated for the free acid); Lit.[12] $[\alpha]_{546}$ -35.1° (calculated for the free acid).

The high yielding regioselective reaction at position 1 with an optically active electrophile solves simultaneously both problems of differentiating key inositol hydroxyl groups and optical resolution at the first stage of the synthetic route. The synthesis of IP_3 here described shows evident advantages over most of previously reported work on the preparation of this biologically important compound. Other interesting inositol phosphates can be prepared by this method. Thus compound **4** is an obvious synthon for the preparation of *myo*-inositol 4-phosphate and 1,4-bis(phosphate). This strategy also permits the entry into the L-series starting from compound **2**.

As a further example of versatility, diacetals **3** and **4** are appropiate starting materials for the direct synthesis of complex glycosyl phosphatidylinositols where *myo*-inositol appears phosphorylated at position 1 and glycosylated at position 6 or 4. These glycosylation reactions are presently been carried out in our laboratory.



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