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FACILE OPTICAL RESOLUTION OF DL-1,4,5,6-TETRA-*O*-BENZYL-*MYO*-INOSITOL: KEY SYNTHONS FOR THE PHOSPHOINOSITIDES

R. Aneja,* and A. Parra

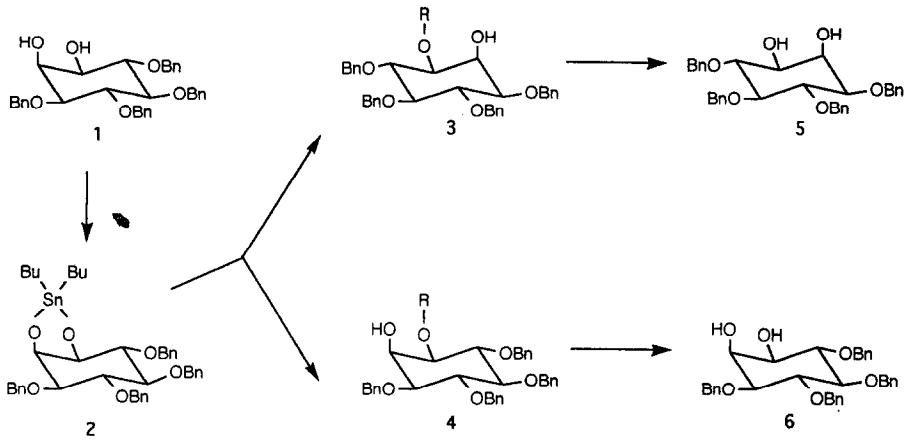
Nutrimed Biotech, Cornell University Research Park
Langmuir Laboratory, Ithaca, NY 14850 USA

Abstract: The facile preparation of 1D-1,4,5,6-tetra-*O*-benzyl-*myo*-inositol and its enantiomer 1L-1,4,5,6-tetra-*O*-benzyl-*myo*-inositol from the corresponding racemate via the 1-(1′S)-(-)-camphanic acid esters is described.

The optical resolution of DL-1,4,5,6-tetra-*O*-benzyl-*myo*-inositol (**1**) was first achieved and the absolute configurations of the enantiomers 1D-1,4,5,6-tetra-*O*-benzyl-*myo*-inositol (**5**) and 1L-1,4,5,6-tetra-*O*-benzyl-*myo*-inositol[1] (**6**) were derived over 20 years ago.[2,3] Over the succeeding years, **5** and **6** have become established as the primary references for correlating the absolute configuration of other asymmetrically substituted *myo*-inositols. Compound **5** has been used as an intermediate, albeit after multi-step conversion into 1L-1,2,4,5,6-penta-*O*-acetyl-*myo*-inositol, for the synthesis of 1D-*myo*-inositol-1-phosphate and *sn*-phosphatidyl-1D-*myo*-inositol.[3a] The enantiomer **6**, in which the free C-1 hydroxyl is available for direct phosphorylation, is potentially more valuable than **5** as a synthon[4] for the preparation of phosphoinositides and inositol phosphates implicated in intracellular signalling and membrane protein anchors.[5] However, the potential of **6** as a synthon has not been realized, in part because an efficient method for its preparation is not available. Methods for the optical resolution requiring derivatization with acetylated monosaccharides to form diastereomeric glycosides of **1** give very low yields.[3] Two recent methods validated for the preparation of **5**, one by a four step sequence of reactions from *myo*-inositol involving transketalization with D-camphor dimethyl ketal as the chiral reagent,[6] and the other from **1** by the kinetically controlled esterification with methyl hydrogen 2,3-cyclohexylidene-D-tartrate,[7] may be adapted for the preparation of **6** but necessitate the repetition of the complete preparative process using chiral reagents of the L-configuration series. We now report the first practical method which gives both **5** and **6** in high purity and good yield.

The new method is based on the regioselective esterification of **1** at the 1(3)-hydroxyl with (1S)-(-)-camphanic chloride, separation of the resulting diastereomeric esters by crystallization or chromatography, and base catalyzed hydrolysis to the enantiomeric diols (Scheme 1). For achieving predominant monoesterification selectively at the equatorial 1(3)-OH versus the axial 2-OH, the reactivity of the stannylene derivatives of vicinal diols[8] was exploited. The dibutylstannylene derivative **2** was prepared from **1** as described.[9] The reaction of **2** in anhydrous ethyl ether containing triethylamine (1.2 equiv), with (1S)-(-)-camphanic chloride (1.0 equiv) at -20°C overnight, addition of water and extraction into chloroform, gave the diastereomeric ester derivatives (**3** + **4**) as the major product. Crystallization twice from acetone-methanol

gave the more polar diastereomer **4**, mp 176-177 °C, $[\alpha]_D$ -21.33° (c 5.1, $CHCl_3$). Chromatography of the mother liquors of crystallization on silica eluted with chloroform - isopropyl ether gave the less polar diastereomer **3**, mp 169-170 °C, $[\alpha]_D$ +14.87° (c 3.55, $CHCl_3$). The assigned structures **4** and **3** are supported *inter alia* by (M+H) = 721 in positive ion FAB MS of each, ^1H NMR signals respectively at δ 4.31 (t, J 2.9Hz) and δ 4.28 (t, J 2.7Hz) assigned to H-C(2)OH, and by the result of base catalyzed hydrolysis. Hydrolysis (LiOH, THF/ water) of **3** and **4** gave respectively **5**, mp 142.5 °C, $[\alpha]_D$ +23.4° (c 4.5, $CHCl_3$), literature[3] mp 140.2-142.1 °C, $[\alpha]_D$ +25.0° (c 0.18, $CHCl_3$); and, **6**, mp 143.0 °C, $[\alpha]_D$ -25.1° (c 5.2, $CHCl_3$), literature[3] mp 141.0-143.0 °C, $[\alpha]_D$ -24.31° (c 1.3, $CHCl_3$). The overall yields of **5** and **6** were 66% and 78% of theoretical.[10] Novel applications developed for **5** and **6** will be reported.[4]



Scheme 1: Only one enantiomer shown for structures **1** and **2**. ROH = (1S)-(-)-camphanic acid.

References and Notes

1. May be named 1D-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol to highlight the structural relationship with the natural phosphoinositides (see NC-IUB, *Eur. J. Biochem.* **1989**, *180*, 485-486).
2. Klyashchitskii, B.A.; Strakhova, G.D; Shvets, V.I.; Sokolov, S.D.; Preobrazhenskii, N.A. *Dokl. Akad. Nauk SSR* **1969**, *185*, 594 (*Proc. Acad. Sci. USSR (Chem.)* **1969**, *185*, 237).
3. a, Shvets, V.I.; Klyashchitskii, B.A.; Stepanov, A.E.; Evstigneeva, R.P. *Tetrahedron* **1973**, *29*, 331-340; b, Stepanov, A.E.; Shvets, V.I.; Evstigneeva, R.P. *Bioorgan. Khim.* **1976**, *2*, 1618-1622.
4. Aneja, R., unpublished.
5. Berridge, M.J. *Annu. Rev. Biochem.* **1987**, *56*, 159-193. Berridge, M.J.; Irvine, R.F. *Nature* **1989**, *341*, 197-205; Ferguson, M.A.J. *Annu. Rev. Biochem.* **1988**, *57*, 289-320.
6. Bruzik, K.S.; Salamonczyk, G.M. *Carbohydrate Res.* **1989**, *195*, 67-73. See also, Bruzik, K.S.; Tsai, M-D. *J. Am. Chem. Soc.* **1992**, *114*, 6361-6374.
7. Watanabe, Y.; Oka, A.; Shimizu, Y.; Ozaki, S. *Tetrahedron Lett.* **1990**, *31*, 2613-2616.
8. Wagner, D.; Verheyden, J.P.H.; Moffat, J.G. *J. Org. Chem.* **1974**, *39*, 24-39.
9. Nasheed, M.A.; Anderson, L. *Tetrahedron Lett.* **1976**, 3503-3506.

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