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1D- and 1L-1,2:4,5-Di-*O*-cyclohexylidene-3-*O*-allyl-*myo*-inositols: Complementary Versatile New Starting Materials for Syntheses in the 1D-*myo*-Inositol Series

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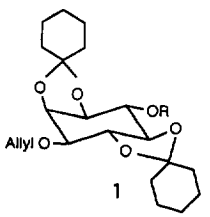
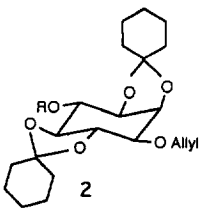
Abstract: The preparation and proof of absolute configuration as 1D- and 1L- respectively are presented for (-)- and (+)-1,2:4,5-di-*O*-cyclohexylidene-3-*O*-allyl-*myo*-inositol, two versatile complementary materials equally suitable for syntheses in the 1D-*myo*-inositol series. Copyright © 1996 Elsevier Science Ltd

Phosphatidyl-*myo*-inositol phosphates and *myo*-inositol phosphates belonging to the 1D- stereochemical series are extremely important intracellular signal transducers.[1] Consequently there is wide interest in optically resolved *myo*-inositol derivatives as starting materials for syntheses.[2] We report on the preparation and absolute configuration of the two enantiomeric 1,2:4,5-di-*O*-cyclohexylidene-3-*O*-allyl-*myo*-inositols (**1**) and (**2**). These were designed as key intermediates in the synthesis of phosphatidyl-1D-*myo*-inositol-3-phosphates,[3] a structural series recently recognized as particularly important in mitogenesis[4,5] and protein kinesis.[6] We now present these enantiomers as versatile chiral starting materials generally appropriate for syntheses in the *myo*-inositol series. Significantly, both the 1D- (**1**) and the 1L- (**2**) enantiomer are equally suitable as complementary synthons for the target 1D- configuration series, and this provides an uncommon economic advantage.



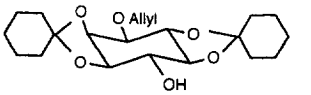
1

1, R=H
3, R=Camph.



2

2, R=H
4, R=Camph.



5

Reaction of highly purified (±)-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol[7] and allyl bromide in DMF at 0-5 °C with gradual addition of NaH as a new protocol providing kinetic control, resulted in highly selective mono-allylation at 3-OH, such that (±)-1,2:4,5-di-*O*-cyclohexylidene-3-*O*-allyl-*myo*-inositol[8] was obtained pure by crystallization without need for liquid chromatography. Esterification of the (±)-3-*O*-allyl derivative

using (1S)-(−)-camphanic acid chloride/NEt_3 and separation of the diastereomeric esters by MPLC on silica and crystallization from acetone gave each of the two diastereomers (>80% yield) in >98% purity as judged by TLC, HPLC and ^1H NMR. Alkali catalyzed hydrolysis of the more polar of the two diastereomeric esters **3**, $[\alpha]_D$ −16.5°, (c 1.5 $CHCl_3$) yielded (−)-**1**, $[\alpha]_D$ −9.5°, (c 1.0, $CHCl_3$). Similar treatment of the less polar diastereomer **4**, $[\alpha]_D$ −2.03°, (c 1.0 $CHCl_3$) gave (+)-**2**, $[\alpha]_D$ +9.17°, (c 0.5, $CHCl_3$).[9]

Reaction of (−)-**1** successively with (i) hot HOAc-H_2O to remove both the *O*-cyclohexylidene protecting groups, and (ii) an excess of NaH and BnBr in anhydrous DMF, gave 1D-3-*O*-allyl-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol, $[\alpha]_D$ −2.3°, (c 1.0, $CHCl_3$). Treatment of the *O*-benzyl derivative with potassium *tert*-butoxide in warm DMSO to isomerize *O*-allyl to *O*-[prop-1′-enyl] followed by methanolic HCl[10] yielded (+)-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol, $[\alpha]_D$ +11.2°, (c 1.1, $CHCl_3$). The absolute configuration of (+)-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol has been unequivocally assigned as 1D-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol.[11] Therefore, the absolute configuration of (−)-**1** is derived unambiguously as 1D-1,2:4,5-di-*O*-cyclohexylidene-3-*O*-allyl-myo-inositol. Similarly, (+)-**2** is assigned the 1L- configuration.

Syntheses in the *myo*-inositol phosphate series involve selective sequential OH protection/deprotection commonly leading to (poly)-*O*-benzyl-*myo*-inositols which are subjected to phosphorylation.[2] In our experience, the allyl[10] is an excellent temporary *O*-protecting group. It is adequately stable to a variety of nucleophilic, acidic and basic reaction conditions needed for introducing and removing several other protecting groups and yet it can be removed cleanly in the presence of *O*-benzyl groups as exemplified in the preceding paragraph. Further, the symmetry plane through C-2 and C-5 in *myo*-inositol mandates that the 1L-3-*O*-allyl derivative (**2**) is identical with 1D-1-*O*-allyl-2,3:5,6-di-*O*-cyclohexylidene-*myo*-inositol (**5**), a complementarily substituted structural isomer of **1**. Overall, the molecular design features, the experimental protocols employed, and the utilization of both the enantiomers make **1** and **2** attractive optically resolved starting materials for synthesis in the 1D- *myo*-inositol series. As example, we have exploited **1** and **2** for syntheses of the complete range of phosphatidyl-*myo*-inositol-3-phosphates and this will be reported separately.

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REFERENCES AND NOTES

1. Berridge, M.J. *Nature* **1993**, *361*, 315-325.
2. Billington, D.C. *The Inositol Phosphates*; VCH Publishers: New York. 1993.
3. Aneja, R.; unpublished.
4. Toker, A.; Meyer, M.; Reddy, K.; Falck, J. R.; Aneja, R.; Aneja, S.; Parra, A.; Burns, D.J.; Cantley, L.M. *J. Biol. Chem.* **1994**, *269*, 32358-32367.
5. Kapeller, R. and Cantley, L. *BioEssays* **1994**, *16*(8), 1-12.
6. Camilli, P. D.; Emr, S. D.; McPherson, P. S.; Novick, P. *Science*, **1996**, *271*, 1533-1539.
7. Aneja, R.; Aneja, S. G.; Parra, A. *Tetrahedron Asymmetry* **1995** (No. 1), 17-18.
8. Shashidhar, M.S.; Keana, F.W.; Volwerk, J.J.; Griffith O.H. *Chem. Phys. Lipids*, **1990**, *53*, 103-113.
9. All new compounds (**1-4**) were characterized fully including high resolution MS and NMR.
10. Gigg, J.; Gigg, R.; Payne, S.; Conant, R. *J. Chem. Soc. Perkin Trans. I* **1987**, 1757-1762.
11. Aneja, R.; Aneja, S.; Pathak, V. P.; Ivanova, P.T. *Tetrahedron Lett.* **1994**, *35*, 6061-6062.

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