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The Absolute Configuration and Optical Purity of (−)- and (+)-1,2:4,5-Di-*O*-cyclohexylidene-*myo*-inositols

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Abstract: The absolute configurations of (−)- and (+)-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositols are derived as 1D- and 1L-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositols respectively, and are reverse of the most recent literature assignments.

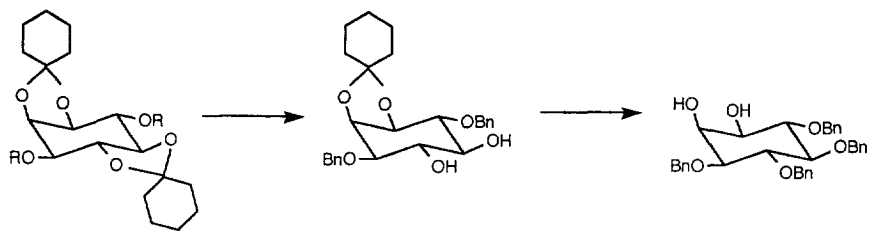
In connection with studies on the cell membrane lipids which mediate a new signalling pathway that involves phosphoinositide 3-kinase (PtdIns 3-kinase) as a pivotal effector enzyme,[1,2] we are interested in several new chiral synthons derived from the known 1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositols.[3,4,5] However, the literature reports on the enantiomeric 1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositols are in discord. Significantly different specific rotation values[6] have been reported for the (−)- as well as the (+)-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositols prepared by two methods.[3,4] Surprisingly, the (−)-[3] and the (+)- enantiomer[4] have been identified as 1D-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol[7] but the basis for each conclusion is equivocal[8] and inadequate for reconciling the converse assignments. We now report experimental data on the transformation of each enantiomer into an established reference of configuration in the *myo*-inositol series and thereby unambiguously derive the absolute configurations for each enantiomer.

Preliminary experiments in the present study indicated that (−)- and (+)-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositols prepared exactly by the published procedures[3,4] and with $[\alpha]_D$ values comparable with the literature[6] are contaminated with structural and stereochemical isomers. Eventually, pure (−)- and (+)- forms were prepared by a modification of the described procedure[4] in which the starting (±)-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol and intermediate bis-3,6-(1′*S*)-(−)-camphanic esters were purified to homogeniety by repeated crystallization from acetone. Alkali catalyzed hydrolysis of the less polar diastereomer of bis-3,6-(1′*S*)-(−)-camphanic ester **1**[9] gave pure (−)-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol **2**.[10] Complete benzylation (BnCl/NaH, DMF) of **2** gave the dibenzyl derivative **3**.[11] The 4,5-*O*-cyclohexylidene group in **3** was selectively removed by transketalization (ethylene glycol, H^+) to obtain **4**.[12] Successive benzylation (BnCl/NaH, DMF) of **4** and acid catalyzed deketalization ($HOAc/H_2O$) gave the product, mp 143.0 °C, $[\alpha]_D$ -25.1 (c 5.2, $CHCl_3$), identified as 1L-1,4,5,6-tetra-*O*-benzyl-*myo*-inositol[13] **5** by direct comparison with an authentic sample, mp and mixed mp 141.0-143 °C, $[\alpha]_D$ -24.31 (c 1.3, $CHCl_3$).[14] Since the absolute configuration of **5** is well established,[14] and the sequence of transformations in Scheme 1 produces very good yields and does not effect the stereochemistry, our data unequivocally derive the absolute configuration of (−)-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol as 1D-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol **2**. This conclusion was corroborated and the (+)-enantiomer of **2**[15] confirmed as 1L-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol by analogous conversion into 1D-1,4,5,6-tetra-*O*-benzyl-*myo*-inositol. These assignments are the reverse of the most recent literature.[4,5]

As a corollary, the 1D-series absolute configurations follow for the two new benzyl derivatives **3** and **4** generated in the correlation sequence, and for other novel synthons prepared from the (−)-enantiomer **2**.

With the crucial issue of absolute configuration settled, we are exploiting **3**, **4**, and other novel chiral derivatives prepared from **2**, in syntheses *inter alia* of phosphatidylinositol-4,5-bisphosphates and phosphatidylinositol-3,4,5-trisphosphates, the phosphoinositide lipids which are involved in signal transduction respectively as substrates and products of PtdIns 3-kinase.[1,2,16]

Scheme 1



1, R = (1′*S*)-(−)-Camphanoyl
2, R = H
3, R = Bn

4

5

References and Notes

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4. Vacca, J. P.; deSolms, S.J.; Huff, J.R.; Billington, D.C.; Baker, R.; Kulagowski, J.J.; Mawer, I.M. *Tetrahedron*, **1989**, *45*, 5679-6702. *ibid.* **1991**, *47*, 907.
5. Billington, D.C. *The Inositol Phosphates*; VCH Publishers: New York. **1993**, pp. 62-64.
6. For the (-)-form, lit.[3] $[\alpha]_D$ -5.6 (c 0.75, $CHCl_3$), lit.[4] $[\alpha]_D$ -16.0 (c 3.15, $CHCl_3$); for the (+)-form, lit.[3] $[\alpha]_D$ +6.5 (c 0.3, $CHCl_3$), lit.[4] $[\alpha]_D$ +15.7 (c 3.65, $CHCl_3$).
7. Named as recommended by Nomenclature Committee, IUB, *Eur. J. Biochem.* **1989**, *180*, 485-486. Other equivalent names have been used earlier e.g., *sn*-1,2:4,5-di-*O*-cyclohexylidene-*myo*-inositol.[3]
8. Preparation from chiral 1,2-cyclohexylidene-*myo*-inositols by acid catalyzed ketalization with cyclohexanone as a basis[3] is ambiguous as concomitant migration of the 1,2-cyclohexylidene to the 2,3-location is tantamount to inversion. The optical rotation of derived *myo*-inositol-1,4-bisphosphates as basis[4] is unreliable as the magnitude is close to zero and the sign of rotation for inositol phosphates is highly dependent on pH (Cosgrove, D.J. *Inositol Phosphates;* Elsevier: New York. **1980**, pp. 57-72).
9. $[\alpha]_D$ +11.6 (c 0.2 $CHCl_3$), lit.[4] $[\alpha]_D$ +9.0 (c 0.2, $CHCl_3$).
10. $[\alpha]_D$ -20.0 (c 2.0, $CHCl_3$). The much lower lit. values[6] indicate partially racemized products.[8]
11. $[\alpha]_D$ -73.9 (c 0.5, $CHCl_3$); HRMS FAB$^+$ m/z 521.2913, calc.521.2903,$(M+H)^+$. ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm 1.45-1.69 (br m, 10 H), 3.33 (dd, 1H), 3.65 (dd, 2H), 3.74 (dd, 1H), 4.01 (m, 1H), 4.33 (ψt, J=4.5, 4.6 Hz, 1H), 4.66, 4.97 (m, 4H), 7.26-7.44 (m, 10H).
12. $[\alpha]_D$ +22.8 (c 1.1, $CHCl_3$); HRMS FAB$^+$ m/z 441.2268, calc. 441.2277 $(M+H)^+$. ^{1}H NMR $CDCl_3$ δ ppm 1.42-1.76 (m, 10 H), 2.68 (br, 1H), 2.72 (br, 1H), 3.39 (ψt, 1H), 3.52 (m, 2 H), 3.95 (ψt, 1H), 4.07 (dd, 1H), 4.31 (t, J 4.2,4.8Hz, 1H), 4.67, 4.97 (dd, 2H), 4.77 (s, 2H).
13. May be named 1D-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol to show the stereochemical relationship with **2**.
14. Aneja, R.; Parra, A. *Tetrahedron Lett.* **1994**, *35*, 525-526, and references therein.
15. $[\alpha]_D$ +21.0 (c 2.0, $CHCl_3$), prepared from the more polar diastereomer of bis-3,6-camphanic ester $[\alpha]_D$ -42.0 (c 0.2 $CHCl_3$), lit.[4] $[\alpha]_D$ -31.0 (c 0.2, $CHCl_3$).
16. Supported by PHS/NIH grant GM49594 (to R.A.). We thank D. Fuller (Cornell) for NMR data.

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