Pergamon

Tetrahedron Letters, Vol. 35, No. 33, pp. 6061-6062, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01298-9

THE ABSOLUTE CONFIGURATION OF (+)-1,2,4,5,6-PENTA-*O*-BENZYL-*MYO*-INOSITOL

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Abstract: The absolute configuration of (+)-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol is correlated with 1D-1,4,5,6-tetra-*O*-benzyl-*myo*-inositol and thus confirmed as 1D-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol.

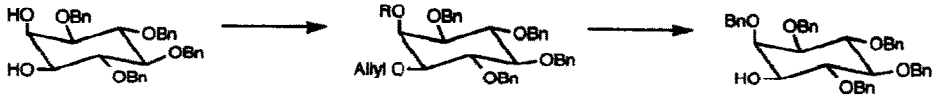
Phosphatidylinositols (PtdIns) and inositol phosphates (InsP) based on 1D-*myo*-inositol are vital mediators, second messengers, and modulators of intracellular signal transduction, and are constituents of the glycosylphosphatidylinositol membrane protein anchors.[1] Hence there is immense interest in their synthesis and in chiral inositol derivatives as synthons.[2,3,4] In this context, the enantiomeric 1,2,4,5,6-penta-*O*-benzyl-*myo*-inositols are highly suitable as intermediates for the synthesis of the parent series of InsP,[5,6] of PtdIns[5,7] as well as their phosphonate and other analogues.[8] The absolute configuration of the (+)-enantiomer was originally proposed as 1D-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol (**4**) based on its conversion into (+)-bornesitol.[5] Recently, two independent X-ray crystal structure analyses have been carried out on the (-)-camphanic acid[9] ester of the (+)- enantiomer.[6,7] Both X-ray studies have deduced the 1L-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol[10] configuration for the (+)- enantiomer, a conclusion which is the reverse of the previous assignment. This disagreement is reflected *inter alia* in the reported conversions of both the (+)- as well as the (-)-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol into the same 1D-*myo*-inositol-1-phosphate by direct phosphorylation followed by debenzylation,[5,6,11] and into phosphatidyl-D-*myo*-inositols by phosphatidylation and debenzylation.[5,7] Moreover, the underlying uncertainty affects other syntheses such as of the glycosylphophatidylinositol membrane anchors,[12] wherein the absolute configuration of crucial *myo*-inositol synthons was derived by correlation with (+)-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol.

We now report our experimental results which allow unambiguous assignment of absolute configuration to the (+)-enantiomer. 1D-1,4,5,6-tetra-*O*-benzyl-*myo*-inositol[4] (**1**, Scheme 1), $[\alpha]_D$ +23.4° (c 4.5, $CHCl_3$), was converted into its 2,3-dibutylstannylene derivative as described for the (±)-compound,[13] and the latter allowed to react with allyl bromide in DMF solution at 80 °C for 18 hours. The major product, m.p. 73-74 °C, $[\alpha]_D$ + 3.21° (c 3.3 $CHCl_3$) was identified as the expected equatorial-*O*-allyl derivative **2** based *inter alia* on the ^{1}H NMR signal at δ 4.22 ppm (1H, t, J= 2.7 Hz, 2.7 Hz) which is characteristic of equatorial H-C(2)OH coupled to the adjacent axial H-C(1) and H-C(3). Treatment of the *O*-allyl derivative **2** in DMF with NaH and benzyl bromide gave the mono-*O*-allyl-penta-*O*-benzyl-*myo*-inositol (**3**), m.p. 72-73 °C, $[\alpha]_D$ -2.6°

(c 2.0, $CHCl_3$); lit.[14] m.p. 71-72 °C, $[\alpha]_D$ -2.2° (c 1, $CHCl_3$) for a compound obtained by benzylation of 1D-3-*O*-allyl-1,2,4-tri-*O*-benzyl-*myo*-inositol. Treatment of **3** with potassium *tert*-butoxide in DMSO followed by methanolic hydrochloric acid removed the allyl residue[14] and yielded (+)-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol (**4**), m.p. 62-63 °C, $[\alpha]_D$ +9.7° (c 1.5, $CHCl_3$); lit.[14] m.p. 64-65 °C, $[\alpha]_D$ +10.0° (c 1, $CHCl_3$). Since the absolute configuration of our starting material is well established as 1D-1,4,5,6-tetra-*O*-benzyl-*myo*-inositol (**1**),[4,5] and the sequence of transformations (Scheme 1) does not effect the stereochemistry, our data unequivocally confirm the absolute configuration of (+)-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol as 1D-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol (**4**). This was corroborated and the (-)- enantiomer of **4** confirmed as 1L-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositol by analogous preparation from the 1L-enantiomer of **1**.

Because optically pure 1D- (**1**) and 1L-1,4,5,6-tetra-*O*-benzyl-*myo*-inositols can be prepared easily,[4] and the three steps in Scheme 1 and the analogous sequence from the 1L-enantiomer give 70 to 90% yield, our data provide advantageous alternative syntheses of 1D- and 1L-1,2,4,5,6-penta-*O*-benzyl-*myo*-inositols.[15]

Scheme 1



References and Notes

1. Berridge, M.J.; Irvine, R.F. *Nature* **1989**, *341*, 197-205; Michell, R.H. *Trends in Biochem. Sci.* **1992**, 274-276. Ferguson, M.A.J. *Annu. Rev. Biochem.* **1988**, *57*, 289-320. Toker A.; Meyer M.; Falck J. R.; Aneja, R.; Aneja, S.; Burns D. J.; Cantley L. M. **1994** *J. Biol. Chem.* Submitted.
2. Billington, D.C. *The Inositol Phosphates*; VCH Publishers: New York. 1993.
3. Bruzik, K.S.; Tsai, M-D. *J. Am. Chem. Soc*, **1992**, *114*, 6361-6374. Ling, L.; Watanabe, Y.; Akiyama, T.; Ozaki, S. *Tetrahedron Lett.* **1992**, *33*, 1911-1914.
4. Aneja, R.; Parra, A.P. *Tetrahedron Lett.* **1994**, *35*, 525-526.
5. Shvets, V.I.; Klyashchitskii, B.A.; Stepanov, A.E.; Evstigneeva, R.P. *Tetrahedron* **1973**, *29*, 331-340.
6. Billington, D.C.; Baker, R.; Kulagowski, J.J.; Mawer, I.M. *J. Chem. Soc. Chem. Comm.* **1987**, 314-316.
7. Garigapati, V.R.; Roberts, M.F. *Tetrahedron Lett.* **1993**, *29*, 769-772.
8. Dreef, C.E.; Douwes, M.; Elie, C.J.J.; van der Marel, G.A.; van Boom. J.H. *Synthesis* **1991**, 443-447. Alisi, M.A.; Brufani, M.; Filocamo, L.; Gostoli, G.; Maiorana, S. *Tetrahedron Lett.* **1992**, *33*, 7793-7796.
9. Gerlach, von H. *Helvetica Chimica Acta* **1985**, *68*, 1815-1821.
10. Named as recommended by Nomenclature Committee, IUB, *Eur. J. Biochem.* **1989**, *180*, 485-486. Equivalent names have been used earlier, e.g., D-2,3,4,5,6-pentabenzylinositol.[7]
11. Ballou, C.E.; Pizer, L.I. *J. Am. Chem. Soc.* **1959**, *81*, 4775-4779.
12. Murakata, C.; Ogawa, T. *Tetrahedron Lett.* **1990**, *31*, 2439-2424. Murakata, C.; Ogawa, T. *Tetrahedron Lett.* **1990**, *32*, 101-104.
13. Nasheed, M.A.; Anderson, L. *Tetrahedron Lett.* **1976**, 3503-3506.
14. Gigg, J.; Gigg, R.;Payne, S.; Conant, R. *J. Chem. Soc. Perkin Trans. 1* **1987**, *1757-1762.*
15. Supported by research grant GM43654 and CA57107 from the N.I.H. (to R.A.). We thank D. Fuller (Cornell) for NMR and R. Reiger (SUNY Stony Brook) for MS data.

(*Received in USA* 20 *May* 1994; *revised* 23 *June* 1994; *accepted* 30 *June* 1994)