Tetrahedron: Asymmetry Vol. 4, No. 10, pp. 2135-2138, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
© 1993 Pergamon Press Ltd

Enzyme Assisted Synthesis of Enantiomerically Pure *myo*-Inositol Derivatives - Chiral Building Blocks for Inositol Polyphosphates

P.Andersch and M.P.Schneider *

FB 9 - Bergische Universität-GH-Wuppertal; 42097 Wuppertal, Germany

(*Received in UK* 19 *July* 1993)

Abstract Using a short and facile synthetic protocol involving highly selective, regio- and enantioselective enzymatic esterifications as key reaction steps, readily available *myo* -inositol is converted into optically pure 1D-1-*O* -butyryl-4,6-*O*-dibenzoyl-*myo*-inositol (-) - **5** , a selectively protected central intermediate for the preparation of numerous inositol phosphates.

Various inositol phosphates and related inositol phospholipids display a wide variety of biological activities, e.g. as second messengers in cell regulation processes[1]. Unfortunately, however , these molecules are only accessible with difficulty either from scarce natural sources or *via* tedious multistep syntheses. Clearly, the elucidation of the biological role of inositol phosphates would be greatly facilitated if these compounds as well as their structural analogues and inhibitors could be made available *via* facile synthetic processes.

Chiral derivatives of *myo*-inositol are among the most important central intermediates for the synthesis of biologically active inositol polyphosphates. Numerous synthetic routes to these molecules, both chemical and enzyme (microbial) assisted have thus been described in the past[2].

Achiral *myo*-inositol is by far the cheapest and most readily available starting material for these molecules and other, achiral or chiral inositols. It would be the starting material of choice provided a simple method for a highly enantioselective differentiation could be found.

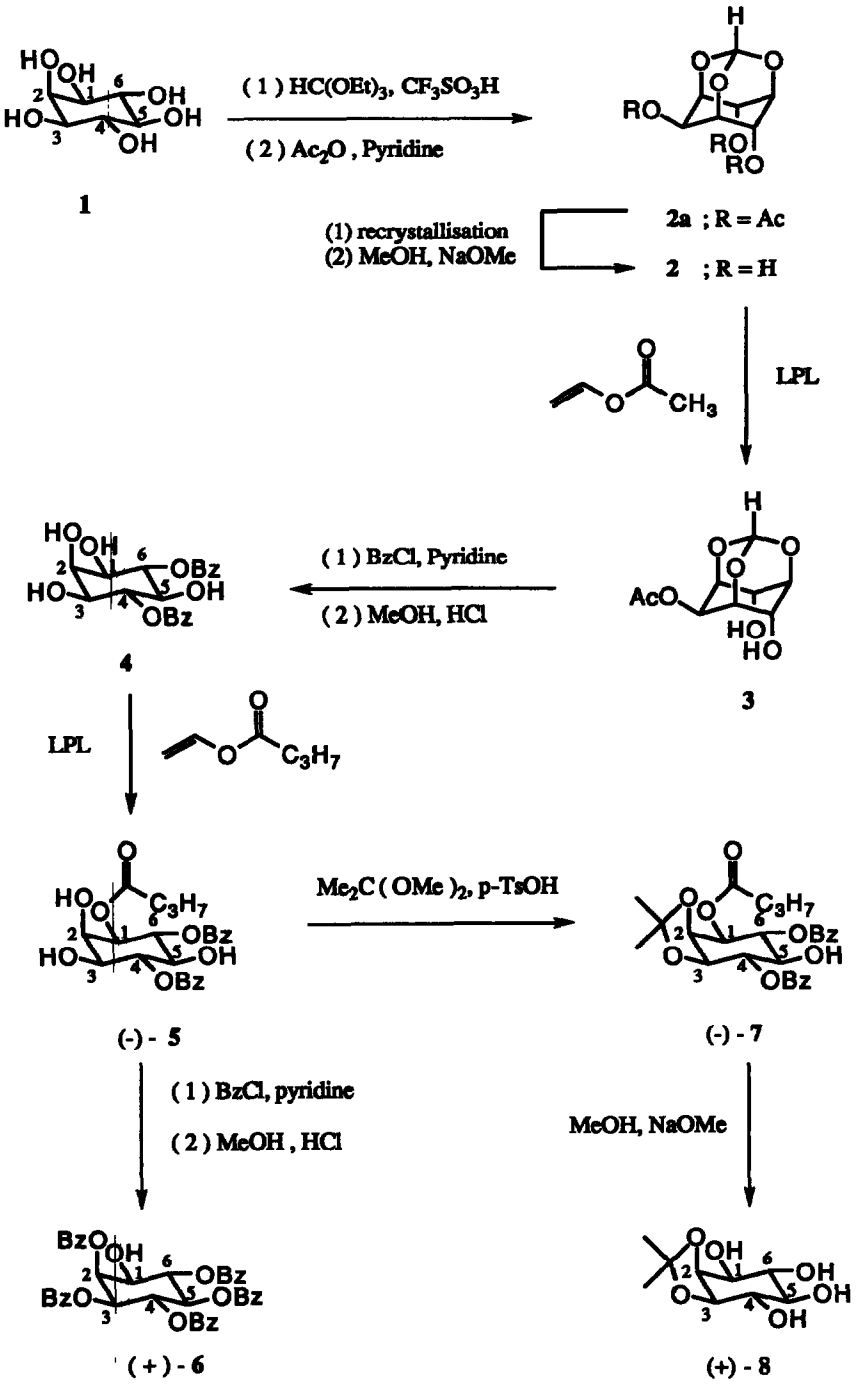
With the aim of making a wide variety of inositols and their polyphosphates in virtually unlimited quantities available for biological studies we decided to develop such a method which should (a) start from readily available *myo*-inositol ; (b) avoid chromatographic purification steps; (c) avoid expensive reagents and exotic protection groups ; (d) lead only to one enantiomer by avoiding the resolution of racemic intermediates or purification of diastereomers.

We wish to report here such a route using regioselective and enantioselective enzymatic transformations as key reaction steps as outlined in Scheme I. The first target was a selectively protected *meso* - derivative of *myo*-inositol which could serve as a central intermediate for the enantioselective, enzymatic transformation. Enantioselective transformations of *meso*- substrates by the differentiation of enantiotopic groups have two important advantages over classical or enzymatic resolutions:

(a) Only one enantiomer is produced in theoretically quantitative chemical and optical yield;

(b) The resulting enantiomer is useful *regardless* of its absolute configuration.

Based on previous approaches[3-5] an improved method - avoiding chromatographic purification steps - for the conversion of *myo* - inositol **1** into " *myo* - inositol orthoformate" **2** was developed. **2** can be obtained *via* this method in 70 % yield and in quantities of 250 g and more. The purification of **2** is conveniently carried out *via* recrystallisation of the corresponding triacetate **2a**.


(1) HC(OEt)3, CF3SO3H
(2) Ac2O, Pyridine
1
2a ; R = Ac
2 ; R = H
(1) recrystallisation
(2) MeOH, NaOMe
LPL
3
(1) BzCl, Pyridine
(2) MeOH, HCl
4
LPL
Me2C(OMe)2, p-TsOH
(-) - 5
(-) - 7
(1) BzCl, pyridine
(2) MeOH, HCl
MeOH, NaOMe
(+) - 6
(+) - 8

Scheme 1

In order to obtain the desired *meso* - derivative **3** with two enantiotopic hydroxy groups in positions 4 and 6 of the inositol backbone, monoprotection of the equatorial hydroxy group in position 2 was required. Chemical methods to this effect proved to be not selective enough[4].

In contrast, completely regioselective monoprotection of the equatorial hydroxy group in **2** was achieved by enzymatic esterification under the conditions of irreversible acyl transfer in presence of lipoprotein lipase from *Pseudomonas sp.* [LPL][6] using numerous different acyl donors. No acylation of the axial hydroxy groups was detectable.

In contrast to experiments described previously[5], enantioselective hydrolyses of numerous diesters derived from derivatives with the general structure of **3** were unsuccessful in our hands and led only to mixtures of products with moderate to poor optical purities. We therefore decided to abandon this route in favour of another *meso*-derivative 4,6-*O*-dibenzoyl - *myo*- inositol **4**. Simple benzoylation of **3** [BzCl, py] , followed by deprotection under strongly acidic conditions [HCl, MeOH] led to **4** in an overall yield of 70 %.

Surprisingly, and only after many unsuccessful attempts we found that **4**, carrying *four different hydroxyl groups* can be transformed conveniently and in *one step* into enantiomerically pure 1D-1-*O*-butyryl -4,6-*O*-dibenzoyl -*myo* - inositol (-) - **5** [$[\alpha]_D^{20}$ = -15, c = 2.0 , EtOAc] by enantioselective , enzymatic esterification using again the same lipoprotein lipase as above.

The absolute configuration of (-) - **5** was determined unambigously by chemical correlation with the known[7] 1D - 1,2,4,5,6 -*O* -pentabenzoyl - *myo*- inositol (-) - **6** [$[\alpha]_D^{20}$ –59.5, c = 1.8 , $CHCl_3$]. The high optical purity [> 95 % e.e] is supported both by comparison of the optical rotations for (+) - **6** [$[\alpha]_D^{20}$ + 60, c = 1.5 , $CHCl_3$], and independently *via* ^{1}H-NMR-experiments with the " Mosher esters " obtained from (-) - **7**.

The 2 - and 3 - hydroxyl groups in (-) - **5** can easily be protected by simple ketalisation [acetone-dimethylacetal, *p*-TsOH] leading to (-) - **7** [$[\alpha]_D^{20}$ - 20, c = 1.0 , AcOEt], which in turn can be deprotected to obtain (+) - **8** [$[\alpha]_D^{20}$ + 44.8, c = 2.0 , MeOH]. Both (-) - **7** and (+) - **8** can be linked with existing routes to enantiomerically pure inositol polyphosphates[2,8,9].

It should be mentioned that all transformations can be carried out on a preparatively useful scale [30 - 150 mmol]. Time consuming chromatographic separation steps are avoided, compounds **2** , **2a** , **3**, **4** and **5** are all crystalline and can be purified by simple recrystallisations. Very inexpensive bulk reagents are used throughout. The lipoprotein lipase used can be immobilized on a variety of carriers and was used for eight consecutive transformations with only moderate loss of activity.

In summary , the above described method allows the conversion of readily available, inexpensive *myo* - inositol *via* a short protocol and in an overall yield of ca. 35 % into enantiomerically pure and selectively protected building blocks for the preparation of many if not all inositol derivatives on a preparatively useful scale. Experiments of this nature are currently under way in our laboratory. The above described experiments also clearly demonstrate once more the power of enzymatic methods as applied to organic syntheses.

Acknowledgements.

We thank the Fonds der Chemischen Industrie for financial support of this work and are grateful to Boehringer Mannheim GmbH, for gifts of enzymes.

REFERENCES

[1] R.H. Gigg, A.H. Haines, B. V. L. Potter (Edit.), *Carbohydr. Res.* , **1992**, *234* , 1 - 268

[2] K.S.Bruzik, M.-D.Tsai, *J.Am.Chem.Soc.*, **1992** , *114* , 6361

[3] H.W.Lee, Y.Kishi, *J.Org.Chem.*, **1985** , *50*, 4402 - 4404

[4] D.C.Billington, R. Baker, J. J. Kulagowski, I. M. Mawer, J. P. Vacca, S. Jane deSolms, J. R. Huff, *J. Chem. Soc. Perkin Trans. I* , **1989** , 1423 - 1429

[5] G. Baudin, B. I. Glänzer, K. S. Swaminathan, A.Vasella , *Helv. Chim. Acta* **1988** , *71* , 1367 - 1378

[6] Lipoprotein lipase from *Pseudomonas species* , Boehringer Mannheim GmbH, Penzberg, Germany

[7] D.Mercier, S.D.Gero, *Tetrahedron Lett.*, **1968** , *31* , 3459 -3462

[8] D.C.Billington, *Chem.Soc.Rev.*, **1989** , *18* , 83 - 122

[9] a) L. Chahoua, M. Baltus, L. Gorrichon, P. Tisnes, C. Zeddo, *J. Org. Chem.*,**1992**, *57*; 5798 - 5801; b) A. Y. Frantova, A. E. Stepanov, A. S. Bushnev, E. N. Zvonkova, V. I. Shvets, *Tetrahedron Lett.* , **1992** , *33* , 3539 - 3542; c) Y.Watanabe, A. Oka, Y. Shimizu, S. Ozaki, *Tetrahedron Lett.* , **1990** , *31* , 2613 - 2616 ; d) D.-M. Gou, C.-S. Chen, *Tetrahedron Lett.* , **1992** , *33* , 721 - 724