ELSEVIER

Carbohydrate Research 308 (1998) 165–168

Note

Racemic 2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate: a versatile intermediate for the preparation of *myo*-inositol phosphates

Tanya Das, Mysore S. Shashidhar *

Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune 411008, India

Received 24 November 1997; accepted in revised form 23 February 1998

Abstract

The versatility of racemic 2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate as an intermediate for the preparation of protected *myo*-inositol derivatives is demonstrated. Procedures described provide simple access to several protected *myo*-inositol derivatives which are intermediates for the preparation of *myo*-inositol phosphates and racemic ononitol. © 1998 Elsevier Science Ltd. All rights reserved

Keywords: Cyclitols; Inositol; Phosphatidylinositol; Signal transduction

The involvement of *myo*-inositol phosphates in cellular signal transduction pathways in living cells of various tissues is now established [1]. The elucidation of mechanisms that govern the *myo*-inositol based signal transduction pathways requires the availability of *myo*-inositol phosphates and their analogues [2–12]. Suitably protected *myo*-inositol derivatives are the key intermediates for the synthesis of phosphorylated inositols and their analogues. We herein describe the preparation of several protected *myo*-inositol derivatives from racemic 2,4-di-*O*-benzoyl-*myo*-inositol 1,3,5-orthoformate (**1**) [13] using simple procedures. Regioselective opening of the orthoester moiety in some *myo*-inositol orthoformate derivatives has been reported [14–16].

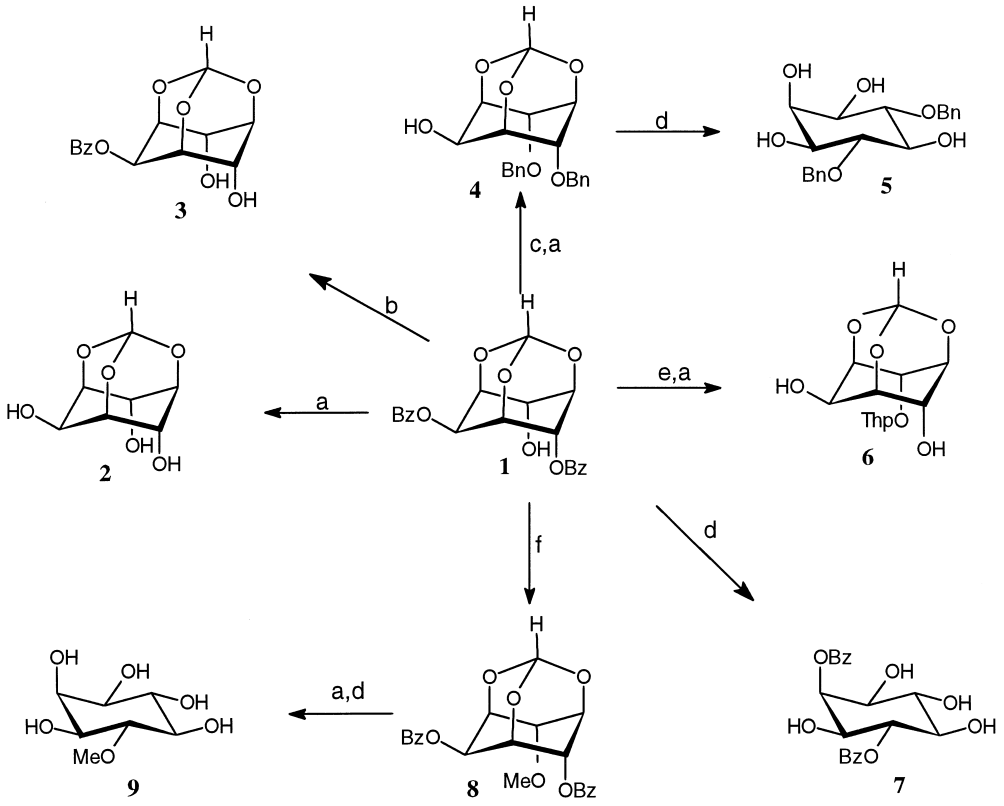
The synthetic utility of the dibenzoate **1** is demonstrated by its conversion to several protected *myo*-inositol derivatives (Scheme 1). The dibenzoate **1**, on refluxing with *tert*-butylamine in methanol, afforded *myo*-inositol orthoformate **2**. Hence this route is an alternative procedure for the preparation of the triol **2** [17–19] without the use of chromatography.

Heating the dibenzoate **1** in 1:5 pyridine–methanol at 50 °C resulted in the preferential solvolysis of the axial 4-benzoate to afford the known diol **3** [20] in 75% yield.

Reaction of the dibenzoate **1** with an excess of benzyl bromide in the presence of an excess of silver (I) oxide yielded the symmetrical 2-*O*-benzoyl-4,6-di-*O*-benzyl-*myo*-inositol 1,3,5-orthoformate [21], which on aminolysis gave the known **4**. Preparation of **4** (from **2**), in 30–50% yield has been reported earlier [17,18] as an intermediate for the synthesis of *myo*-inositol-2-phosphate as

* Corresponding author. Fax: 91-212-33 51 53; e-mail: shashi@dalton.ncl.res.in

PII S0008-6215(98)00061-5



Scheme 1. Reagents and conditions: (a) *tert*-Butylamine, MeOH, reflux. (b) Pyridine, MeOH, 50 °C. (c) DMF, Ag_2O, Benzyl bromide. (d) *p*-toluenesulfonic acid, MeOH. (e) CH_2Cl_2, pyridium *p*-toluenesulfonate dihydropyran [21]. (f) DMF, Ag_2O, ICH_3 [21].

well as *scyllo*-inositol. The present procedure gives the symmetrical diether **4** in an overall yield of 74% starting from the dibenzoate **1** (33% from *myo*-inositol). Removal of the orthoformate moiety in **4** affords the 1,2,3,5-tetrol **5**. The preparation of D-*myo*-inositol-1-phosphate from **5** has been reported previously [22].

The free 6-hydroxyl group of the dibenzoate **1** could be protected as the corresponding tetrahydropyranyl ether [21] which on aminolysis with *tert*-butylamine in methanol afforded the 2,4-diol **6**.

Methanolysis of the dibenzoate **1** in the presence of *p*-toluenesulfonic acid gave the tetrol **7** in excellent yield. None of the steps (starting from *myo*-inositol) involve column chromatography or any expensive reagent. Meek et al. [23] have prepared the tetrol **7** from 3,6-di-*O*-benzoyl-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol in two steps (overall yield 18%.

The dibenzoate **1** could be converted into the corresponding methyl ether **8** using methyl iodide and silver (I) oxide in 80% yield [21]. The benzoate groups in **8** were then removed by reaction with *tert*-butylamine and the orthoformate moiety was removed using *p*-toluenesulfonic acid–methanol to obtain racemic ononitol **9** [24].

In conclusion, the results presented provide convenient access to several known *O*-protected *myo*-inositol derivatives, which can be converted to the corresponding *myo*-inositol phosphates using procedures available in the literature.

1. Experimental

General methods.—For general experimental conditions and procedures for the preparation of 2-*O*-benzoyl-4,6-di-*O*-benzyl-*myo*-inositol 1,3,5-orthoformate, the methyl ether **8** and 2,4-di-*O*-benzoyl-6-*O*-tetrahydropyranyl-*myo*-inositol 1,3,5-orthoformate (mixture of diastereomers) see ref. [21]. The dibenzoate **1** was prepared as reported earlier [13]. Anhyd *p*-toluenesulfonic acid [25] was prepared according to lit. All the compounds previously reported were characterized by comparison of their mp, IR and NMR spectroscopic data with those available in the literature.

Preparation of myo-*inositol 1,3,5-orthoformate* (**2**).—The dibenzoate **1** (1.64 g, 4.1 mmol) was

refluxed in MeOH (44 mL) with *tert*-butylamine (2.2 mL, 20.5 mmol) for 3 h. The product was crystallized from MeOH (0.78 g, 100%). mp 300–301 C°, lit. 300–302 °C [17].

Preparation of 2-O-*benzoyl*-myo-*inositol 1,3,5-orthoformate* (**3**).—The dibenzoate **1** (1.5 g, 3.8 mmol) was heated with pyridine (18 mL) in MeOH (90 mL) for 24 h at 50 °C. The reaction mixture was allowed to attain room temperature and the solvent evaporated. The residue was crystallized (MeOH–$CHCl_3$) to obtain the diol **3** (0.58 g, 53%), mp 210–213 °C, lit. 202–204 °C [20]. A further quantity of **3** (0.24 g, 22%) could be obtained by silica gel column chromatography of the mother liquor (eluent: 30% EtOAc–light petroleum) along with some triol **2** (0.09 g, 13%).

Preparation of 4,6-di-O-*benzyl*-myo-*inositol 1,3,5-orthoformate* (**4**).—2-*O*-benzoyl-4,6-di-*O*-benzyl-*myo*-inositol 1,3,5-orthoformate (0.47 g, 1.0 mmol) was refluxed with *tert*-butylamine (0.8 mL) and MeOH (10 mL) for 20 h. The solvent was removed under reduced pressure and the residue was purified by crystallization from $CHCl_3$–light petroleum mixture (0.34 g, 92%), mp 124–125 °C, lit. 125 °C [18].

Preparation of 4,6-di-O-*benzyl*-myo-*inositol* (**5**).—The crude dibenzyl ether **4** (0.83 g, 2.3 mmol) prior to crystallization was dissolved in MeOH (20 mL) and stirred at room temperature with *p*-toluenesulfonic acid (0.4 g) for 24 h. The pure product was obtained by column chromatography over silica gel (R_f 0.4 in EtOAc) (0.75 g, 93%), mp 137–138 °C, lit. 138.5–139 °C [18].

Preparation of 4-O-*tetrahydropyranyl*-myo-*inositol 1,3,5-orthoformate* (**6**).—2,4-Di-*O*-benzoyl-6-*O*-tetrahydropyranyl-*myo*-inositol 1,3,5-orthoformate (0.33 g, 0.7 mmol) was refluxed in MeOH (8 mL) with *tert*-butylamine (0.6 mL) for 9 h. The product (mixture of diastereomers) was purified by column chromatography over silica gel (1:1 EtOAc–light petroleum) (0.17 g, 91%), mp 201–203 °C. IR: 3160–3380 cm^{-1}. ^{1}H-NMR: (200 MHz, $CDCl_3$–Me_2SO-d_6) 1.5–1.9 (m, 6 H, CH_2 X 3), 3.1–3.4 (broad s, D_2O exchangeable, OH), 3.5–3.7 (m, 1 H), 3.8 (d, 1 H, D_2O exchangeable, OH, *J* 7 Hz), 3.8–4.0 (m, 1 H), 4.0–4.3 (m, 3 H), 4.3–4.6 (m, 2 H), 4.6–4.8 (m, 2 H), 5.5 (s, 1 H, O_3CH). Anal. Calcd for $C_{12}H_{18}O_7$: C, 52.55, H, 6.57; found: C, 52.90, H, 6.26.

Preparation of racemic 2,4-di-O-*benzoyl*-myo-*inositol* (**7**).—The dibenzoate **1** (0.4 g, 1.0 mmol) was dissolved in CH_2Cl_2 (4 mL) and MeOH (4 mL) and anhyd *p*-toluenesulfonic acid (0.04 g, 0.2 mmol) was added and the reaction mixture stirred for 40 h at room temperature. The solvent was then evaporated and the residue purified by filtration over a short column of silica gel (1:1 EtOAc–light petroleum) to give the tetrol **7** (0.36 g, 93%). mp 193–195 °C, lit. 198–201 °C [23].

Preparation of racemic 4-O-*methyl*-myo-*inositol (ononitol)* (**9**).—The methyl ether **8** (0.42 g, 1.0 mmol) was stirred with *tert*-butylamine (0.8 mL) in MeOH (1O mL) at room temperature for 19 h and the product obtained (0.25 g) was treated with *p*-toluenesulfonic acid (0.14 g, 0.74 mmol) and MeOH (8 mL) as in the preparation of the tetrol **5**. Crude **9** was purified by silica gel column chromatography (1:9 MeOH–EtOAc) (0.19 g, 98%). mp 165–168 °C, lit. 165–166 °C [24].

Acknowledgements

Financial support from the DST, New Delhi, is gratefully acknowledged. T.D. thanks UGC, New Delhi, for a fellowship.

References

[1] M.J. Berridge and R.F. Irvine, *Nature*, 341 (1989) 197–205.
[2] S. Ozaki and L. Lei, *Chemo-enzymatic Synthesis of Optically Active myo-Inositol Phosphates*, in Z.J. Witczak and K.A. Nieforth (Eds.), *Carbohydrates in Drug Design*, Marcel Dekker, New York, 1997, pp 343–384.
[3] K.S. Bruzik, *Phosphatidylinositol—Specific Phospholipase C as a Target for Drug Design*, in Z.J. Witczak and K.A. Nieforth (Eds.), *Carbohydrates in Drug Design*, Marcel Dekker, New York, 1997, pp 385–432.
[4] B.V.L. Potter and D. Lampe, *Angew. Chem. Int. Ed. Eng.*, 34 (1995) 1933–1972.
[5] J.J. Kiddle, *Chem. Rev.*, 95 (1995) 2189–2202.
[6] M.S. Shashidhar, *Proc. Indian Acad. Sci. (Chem. Sci.)*, 106 (1994) 1231–1251.
[7] K.S. Bruzik and M.-D. Tsai, *Bioorg. Med. Chem.*, 2 (1994) 49–72.
[8] S.L. Becauge and R.P. Iyer, *Tetrahedron*, 49 (1993) 10441–10448.
[9] D.C. Billington, *The Inositol Phosphate Chemical—Synthesis and Biological Significance*, VCH, New York, 1993.
[10] T. Hudlicky and M. Cebulak, *Cyclitols and Their Derivatives: A Handbook of Physical, Spectral and Synthetic Data*, VCH, New York, 1993.

[11] F. Kaufman, D.J.R. Massy, W. Pirson, and P. Wyss, *Inositol Phosphates and Derivatives: Synthesis, Biochemistry and Therapeutic Potential*, in A.B. Reitz (Ed.), *ACS Symp. Ser. 463*, 1991, pp 202–253.
[12] D.C. Billington, *Chem. Soc. Rev.*, 18 (1989) 83–122.
[13] T. Banerjee and M.S. Shashidhar, *Tetrahedron Lett.*, 35 (1994) 8053–8056.
[14] I.H. Gilbert and A.B. Holmes, *Tetrahedron Lett.*, 31 (1990) 2633–2644.
[15] I.H. Gilbert, A.B. Holmes, M.J. Pestchanker, and R.C. Young, *Carbohydr. Res.*, 234 (1992) 117–130.
[16] S.-M. Yeh, G.H. Lee, Y. Wang, and T.-Y. Luh, *J. Org. Chem.*, 62 (1997) 8315–8318.
[17] H.-W. Lee and Y. Kishi, *J. Org. Chem.*, 50 (1985) 4402–4404.
[18] D.C. Billington, R. Baker, J.J. Kulagowski, I.M. Mawer, J.P. Vacca, S.J. deSolms, and J.R. Huff, *J. Chem. Soc. Perkin Trans.*, I (1989) 1423–1429.
[19] G. Baudin, B.I. Glanzer, K.S. Swaminathan, and A. Vasella, *Helv. Chim. Acta.*, 71 (1988) 1367–1378.
[20] S. Ozaki, Y. Koga, L. Ling, Y. Watanabe, Y. Kimura, and M. Hirata, *Bull. Chem. Soc. Jpn.*, 67 (1994) 1058–1063.
[21] T. Das and M.S. Shashidhar, *Carbohydr. Res.*, 297 (1997) 243–249.
[22] K. Laumen and O. Ghisalba, *Biosci. Biotech. Biochem.*, 58 (1994) 2046–2049.
[23] J.L. Meek, F. Davidson, and F.W. Hobbs Jr., *J. Am. Chem. Soc.*, 110 (1988) 2317–2318.
[24] B.A. Klyaschitskid, A.K. Starostina, L.F. Linberg, V.I. Shvets, and R.P. Evstigneeva, *Zh. Org. Khim.*, 7 (1971) 492–497.
[25] D.D. Perrin and L.F. Armarego, *Purification of Laboratory Chemicals*, Pergamon Press, Oxford, 1992.