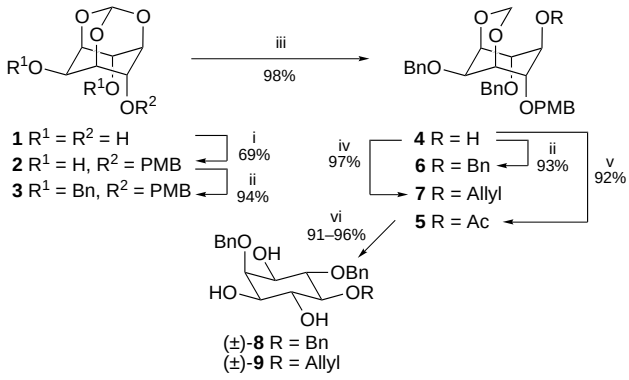
Versatile synthesis of *myo*-inositol phospholipid precursors

Simon J. A. Grove,[a] Ian H. Gilbert,[a] Andrew B. Holmes,*[a,b] Gavin F. Painter[a,b] and Malcolm L. Hill[c]

[a] *Cambridge Centre for Molecular Recognition, Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, UK CB2 1EW*
[b] *Melville Laboratory for Polymer Synthesis, Department of Chemistry, University of Cambridge, Pembroke Street, Cambridge, UK CB2 3RA*
[c] *GlaxoWellcome, Medicines Research Centre, Gunnels Wood Road, Stevenage, UK SG1 2NY*

Homochiral *myo*-inositol derivatives 16 and 20 and their corresponding enantiomers possessing either the natural or unnatural ring stereochemistry for inositol phospholipids are synthesised from *myo*-inositol derivatives 8 and 9 respectively using camphor dimethyl acetals in a resolution–protection sequence.

The biological importance of various inositol phosphates and inositol phospholipids in cell signal transduction and related processes is well documented.[1] In most cases these compounds are not readily available in any quantity from natural sources owing to their low cellular concentrations.[2] Consequently their synthesis[3] has received extensive attention in recent years. Despite this effort many inositol derivatives are still not readily available, owing in part to the lack of availability of suitably protected homochiral *myo*-inositol derivatives.[4] Here we present concise routes to differentially protected ring enantiomers of *myo*-inositol compounds which are suitable starting materials for the synthesis of *myo*-inositol phospholipids.



Scheme 1 *Reagents and conditions*: i, NaH, *p*-$MeOC_6H_4CH_2Cl$ (PMBCl), DMF, 0 °C to room temp.; ii, NaH, BnBr, DMF, 0 °C to room temp.; iii, DIBAL-H (2.5 equiv.), CH_2Cl_2–hexanes, 0 °C to room temp.; iv, NaH, allyl bromide, DMF, 0 °C to room temp.; v, Ac_2O, DMAP, pyridine, room temp.; vi, HCl, MeOH, reflux.

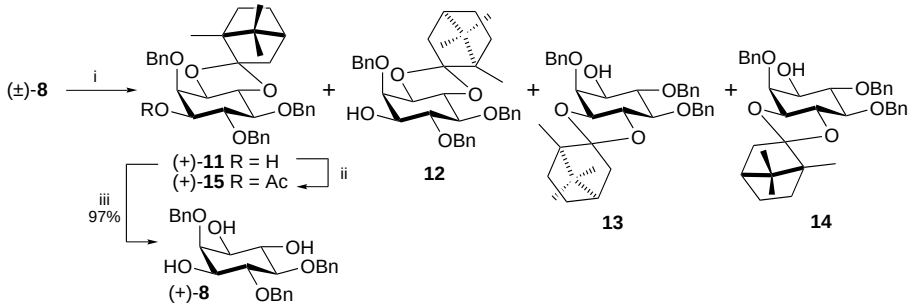
The readily available triol **1**[5] was chemoselectively *p*-methoxybenzylated[6] to give the diol **2** which was then benzylated to afford the fully protected derivative **3** (Scheme 1).† A regioselective DIBAL-H reduction[7,8] of the orthoformate **3** furnished the liberated alcohol **4** as a single isomer in high yield, the structure of which was confirmed by NMR experiments performed on the acetate **5**. Benzylation or allylation of the alcohol **4** afforded the required intermediates **6** and **7**, respectively. Acidic hydrolysis resulted in the simultaneous cleavage of the acetal and *p*-methoxybenzyl ether groups to give the racemic triols **8**[9] and **9** in overall yields of 58 and 56%, respectively, from the triol **1**.

Treatment[4] of **8** with (1*R*)-(+)-camphor dimethyl acetal **10** afforded a diastereoisomeric mixture of acetals **11**–**14** (Scheme 2). This procedure allowed simultaneous protection–resolution of (±)-**8**.

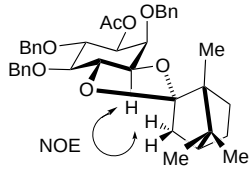
From this mixture the acetal (+)-**11** was isolated by flash chromatography in a yield of 31%, and the remaining acetals were obtained in a combined yield of 59%. The stereochemistry of the acetal (+)-**11** was determined by chemical correlation and NMR experiments. Mild acid hydrolysis (MeOH–AcCl) afforded the triol (+)-**8**,[10,11] which corresponds to the unnatural ring configuration for inositol phospholipids.

Acetylation of the hydroxy group of (+)-**11** gave the acetate (+)-**15** for which a positive NOE was observed between the signal due to the D-1-inositol ring proton and that of the camphor 3′-H_{endo} methylene proton in the ^1H NMR spectrum. Since no enhancement of the methyl resonances was observed upon irradiation of the D-1-inositol ring proton, the stereochemistry of **15** was assigned as 1D-1-*O*-*endo*-6-*O*-*exo* (Fig. 1).

The chromatographically inseparable mixture of acetals enriched in **13** and **14** is also a source of (−)-**11** (Scheme 3).

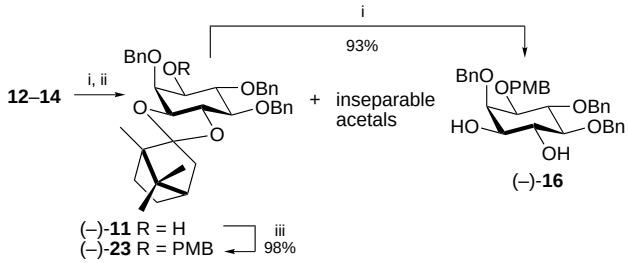


Scheme 2 *Reagents and conditions*: i, (+)-**10** (2.3 equiv.), TsOH (cat.), CH_2Cl_2, reflux; ii, Ac_2O, DMAP, pyridine, room temp.; iii, AcCl, CH_2Cl_2–MeOH (2 : 1)



(+)-**15**

Fig. 1 Assignment of relative stereochemistry of the acetal (+)-**15** by NOE measurement

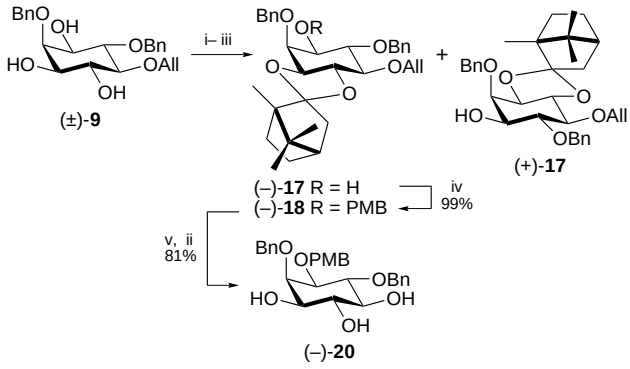


Scheme 3 *Reagents and conditions*: i, AcCl, CH_2Cl_2–MeOH (2:1); ii, (−)-**10**, TsOH, CH_2Cl_2, reflux; iii, NaH, PMBCl, DMF

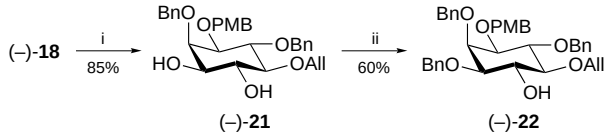
Hydrolysis of the mixture, followed by reacetalisation with the *enantiomeric* camphor dimethyl acetal (−)-**10** afforded after purification (−)-**11** in 40% yield (25% from racemic **8**). *p*-Methoxybenzylation of (−)-**11** gave the PMB ether (−)-**23** which yielded the diol (−)-**16**[10] on mild acidic hydrolysis. The diol (−)-**16** contains a suitable functional group array for elaboration to PtdIns(3,4)P_2.

In a similar protection–resolution sequence using the 5-allyloxy-1,3,4-triol **9**, the enantiomeric acetals (−)-**17** and (+)-**17** were obtained in 27 and 24% yield, respectively, (Scheme 4). *p*-Methoxybenzylation of the 1-hydroxy group of (−)-**17** gave (−)-**18**. Cleavage of the 5-allyloxy and 3,4-acetal groups gave (−)-**20**.[11] The triol **20** is a suitable precursor for elaboration to PtdIns(3,4,5)P_3.

Finally, mild acidic hydrolysis of the 3,4-acetal (−)-**18** afforded the diol (−)-**21** (Scheme 5). Monobenzylation of the 3-hydroxy group using Gigg's procedure[12] (dibutytin oxide, Bu_4NBr and BnBr) furnished the 4-alcohol (−)-**22** in 60% yield. Cleavage of the 5-allyloxy ether would then lead to a suitable precursor for the preparation of PtdIns(4,5)P_2.



Scheme 4 *Reagents and conditions*: i, (−)-**10**, TsOH, CH_2Cl_2, reflux, then separate; ii, AcCl, CH_2Cl_2–MeOH (2:1); iii, (+)-**10**, TsOH, CH_2Cl_2, reflux; iv, NaH, PMBCl, DMF; v, $(Ph_3P)_3RhCl$, DABCO, EtOH–toluene–H_2O (7:3:1), reflux



Scheme 5 *Reagents and conditions*: i, AcCl, CH_2Cl_2–MeOH (2:1); ii, Bu_2SnO, Bu_4NBr, BnBr, MeCN, reflux

In conclusion, the combination of a *meso* starting material, high yielding protection–deprotection sequences and especially a combined resolution–protection strategy, involving the camphor acetals **10**, provides ready access to a number of *myo*-inositol phospholipid precursors. In the accompanying communication we describe the reduction of this concept to practice.

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Footnotes and References

* E-mail: abh1@cus.cam.ac.uk

† All new compounds exhibited satisfactory spectroscopic and analytical data. *Selected data* (*J* values in Hz) for (−)-**16**: mp 153–154 °C; $[\alpha]_D^{22}$ −14.9 (*c* 1.6 in $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 7.39–7.23 (17 H, m), 6.86–6.83 (2 H, m), 5.04 (1 H, d, *J* 11.5), 4.94 (1 H, d, *J* 10.7), 4.93 (1 H, d, *J* 11.2), 4.82 (1 H, d, *J* 10.8), 4.75 (1 H, d, *J* 11.5), 4.67–4.60 (3 H, m and 1 H, t, *J* 9.4), 3.98 (1 H, t, *J* 2.6), 3.82 (1 H, td, *J* 9.6, 2.0), 3.80 (3 H, s), 3.46 (1 H, dd, *J* 9.8, 2.4), 3.36 (1 H, ddd, *J* 9.7, 7.8, 3.8), 3.31 (1 H, t, *J* 9.2), 2.42 (1 H, d, *J* 2.1), 2.25 (1H, d, *J* 7.8). For (−)-**20**: mp 136 °C; $[\alpha]_D^{22}$ −5.9 (*c* 1.6 in $CHCl_3$); δ_H(400 MHz; $CDCl_3$) 7.34–7.23 (12 H, m), 6.86–6.83 (2 H, m), 5.03 (1 H, d, *J* 11.5), 4.97 (1 H, d, *J* 11.2), 4.74 (1 H, d, *J* 11.2), 4.66 (1 H, d, *J* 11.5), 4.62 (2 H, s), 3.99 (1 H, t, *J* 2.6), 3.82 (1 H, t, *J* 9.4), 3.80 (3 H, s), 3.73 (1 H, br t, *J* 9.4), 3.44 (1 H, dd, *J* 9.7, 2.4), 3.38–3.33 (2 H, m), 2.95 (1 H, br s), 2.72 (1 H, br s), 2.46 (1 H, d, *J* 7.9).

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