Ready routes to key *myo*-inositol component of GPIs employing microbial arene oxidation or Ferrier reaction

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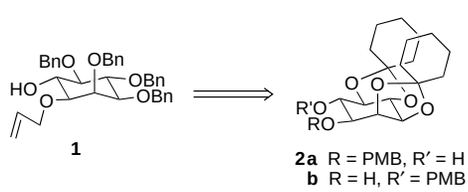
COMMUNICATION

Microbial arene oxidation or Ferrier reaction of enol acetates provides versatile complementary routes that greatly facilitate preparation of inositol synthon(s) for GPI assembly.

It was apparent that glycosylphosphatidylinositols (GPIs) had a special place in glycobiology[1] even before the first assignment of covalent structure to a member of this relatively new class of biomolecules by Ferguson and co-workers.[2,3] Although over 100 proteins/enzymes have now been identified[4] that are anchored to cell surfaces by GPIs, answers to the question 'What do GPIs do?' continue to be evasive.[5] Despite having a central 'conserved core',[6] the *glyco* domains of GPIs show impressive variations, as may be judged by comparing structures from *Trypanosoma*,[3] rat brain Thy-1[7] and *Leishmania*.[8] The inositol moiety is more uniform; however, in our recently completed synthesis of the rat brain Thy-1 anchor,[9] the preparation of the inositol glycosyl acceptor **1**[10] caused the most angst of the entire project.[11] We have therefore been examining other routes that make the universal component **1** more accessible. We report herein on two of them.

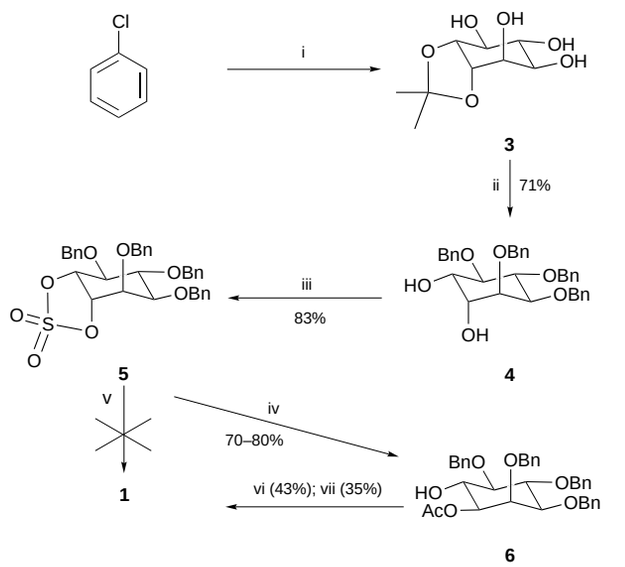
Our original route[12] employed a plan where the regioisomers **2a** and **2b**, prepared from *myo*-inositol, were independently processed to give optically active **1** (Scheme 1). As an alternative, we were attracted to tetrol **3** whose ready preparation from chlorobenzene *via* microbial oxidation has been elegantly explored by Hudlicky *et al*.[13] The axial OH of the routinely prepared derivative **4** had to be inverted, but attempts to facilitate this by selectively protecting the equatorial OH were not encouraging.



Scheme 1

On the other hand, the Sharpless-inspired[14] cyclic sulfate **5**, obtained in excellent yield from **4** (Scheme 2), reacted with caesium acetate to give **6**. Unfortunately a comparable reaction, which would have led directly to **1**, could not be effected with an allyloxy nucleophile. However, deacetylation of **6** and treatment of the resulting diol with 1 equiv. of allyl bromide did afford **1**, albeit accompanied by *ca*. 12% of the regioisomeric allyl ether.

The second route to **1** was based on Bender's discovery[15] that enol esters undergo the Ferrier reaction[16] with excellent stereocontrol. Prestwich had already tested the procedure with the tri-*O*-*p*-methoxybenzyl analog of **8**.[17] Accordingly, methyl α-D-glucopyranoside **7** was converted into **8** by four standard operations in 80% overall yield, and transformation to enol acetate **9** was readily achieved.The Ferrier reaction afforded **10**, isolated in 63% yield, and chelation controlled reduction gave **11** and thence triol **12** (Scheme 3).



Scheme 2 *Reagents and conditions*: i, ref. 13; ii, BnBr, NaH, DMF, Bu_4NI, then AcOH, H_2O, 70 °C, 1 h; iii, $SOCl_2$, Et_3N, 0 °C, 20 min, then $RuCl_3$, $NaIO_4$, 0 °C, 1 h; iv, CsOAc, DMSO, 50 °C, 10–20 min, then THF, H_3O^+, 1 h; v, NaOAll, AllOH; vi, NaOMe, MeOH; vii, AllBr (1 equiv.), NaH, DMF, Bu_4NI, 0 °C

We now had to differentiate between the three hydroxy groups of **12**. Bearing in mind David's precedent with galactose derivatives,[18] triol **12** was subjected to stannylene-mediated derivatization, whereby the allyl group was selectively installed at the desired C1 site of **13** in 75% yield based on recovered **12**, along with small amounts of diallylated products.

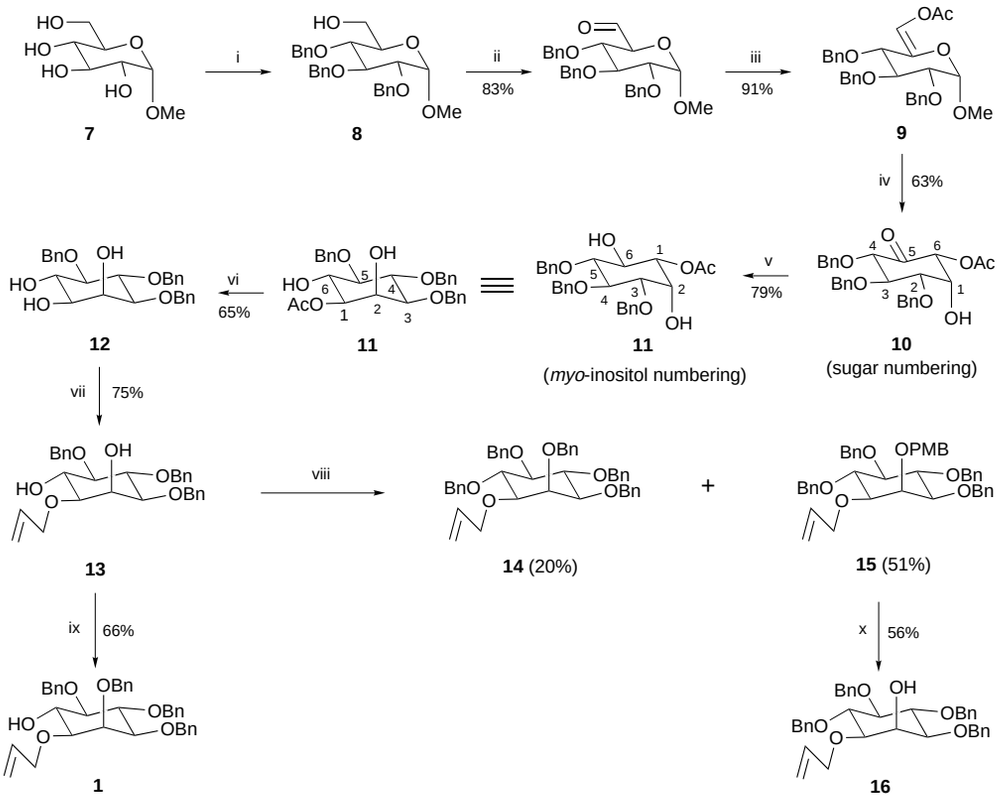
Benzylation of the axial C2 OH was now necessary, and in keeping with standard protocol, **13** was treated with 1 equiv. of *p*-methoxybenzyl chloride (PMBCl), followed by excess BnBr to give compound **14** along with a mono-PMB-containing derivative. That the latter was **15** became evident when oxidative cleavage yielded **16** instead of the expected, known isomer **1**.[10]

The reactivity of the hydroxy groups of **13** was therefore the reverse of the usual axial *versus* equatorial expectation. Indeed, treatment of **13** with 1 equiv. of BnBr gave **1** directly in 66% unoptimized yield.

Experimental

1-*O*-Allyl-3,4,5-tri-*O*-benzyl-D-*myo*-inositol 13

A mixture of triol **12** (994 mg, 2.21 mmol) and bis(tributyltin) oxide (660 mg, 2.65 mmol) in benzene (25 ml) was refluxed for 20 h, with a Dean–Stark trap. Tetrabutylammonium iodide (815 mg, 2.21 mmol) and allyl bromide (956 μl, 11.05 mmol) were added. The mixture was stirred at 70 °C under Ar for 2 h. The solvent was evaporated *in vacuo*. Flash chromatography of the residue gave **13** (387 mg, 0.790 mmol) as a solid in 75% yield [based on recovered triol **12** (520 mg, 1.16 mmol)]. R_f (1 : 1 light petroleum–EtOAc) 0.54; ^{1}H NMR (400 MHz; $CDCl_3$: δ 7.37–



Scheme 3 *Reagents and conditions*: i, ref. 16; ii, DCC, DMSO, TFA, Py, iii, Ac_2O, K_2CO_3, MeCN; iv, $Hg(OAc)_2$, acetone, H_2O; v, $NaBH(OAc)_3$, AcOH, MeCN; vi, NaOMe, MeOH; vii, Bu_2SnO, PhH, reflux, then AllBr, Bu_4NI, 70 °C; viii, PMBCl (1 equiv.), NaH, Bu_4NI, DMF, 0 °C, 2 h, then BnBr (3 equiv.), room temp.; ix, BnBr (1 equiv.), NaH, Bu_4NI, DMF, −5 to 0 °C, 1–2 h; x, CAN, CH_2Cl_2, MeCN, H_2O

7.22 (m, 15H), 5.97–5.87 (m, 1H, allyl), 5.28 (ddd, *J* 17.2, 3.2, 1.6, 1H, allyl), 5.19 (ddd, *J* 10.4, 2.8, 1.2, 1H, allyl), 4.92–4.81 (m, 4H, Bn ×2), 4.72 (s, 2H, Bn), 4.22 (dd, *J* 2.6, 2.8, 1H), 4.21–4.08 (m, 2H, allyl), 4.02 (dd, *J* 9.4, 9.2, 1H), 3.96 (dd, *J* 9.6, 9.6, 1H), 3.42 (dd, *J* 9.6, 2.8, 1H), 3.35 (dd, *J* 9.4, 9.2, 1H), 3.15 (dd, *J* 9.4, 2.8, 1H), 2.63 (s, 1H, OH), 2.55 (s, 1H, OH); ^{13}C NMR: δ 138.6 (s, Bn ×2), 137.8 (s, Bn), 134.4 (d, allyl), 128.4–127.5 (d, Bn ×3), 117.7 (t, allyl), 82.8, 80.8, 79.9, 78.8, 72.1 and 66.9 (d, C1, C2, C3, C4, C5 and C6), 75.8, 75.3, 72.6 and 71.2 (t, Bn ×3 and allyl).

1-*O*-Allyl-2,3,4,5-tetra-*O*-benzyl-D-*myo*-inositol 1

A mixture of diol **13** (600 mg, 1.22 mmol), NaH (60% in mineral oil, 195 mg, 4.88 mmol) and tetrabutylammonium iodide (450 mg, 1.22 mmol) in anhydrous DMF (40 ml) was chilled in an ice bath and covered by Ar. To the stirred mixture was added benzyl bromide (160 µl, 1.34 mmol). After stirring for 2 h at 0 °C, the reaction was quenched with methanol. The mixture was evaporated *in vacuo*. Flash chromatography of the residue gave **1** (470 mg, 0.81 mmol) as a crystalline material in 66% yield. R_f (4:1 light petroleum–EtOAc) 0.36; ^{1}H and ^{13}C NMR ($CDCl_3$) data were identical to those reported in ref. 10.

Acknowledgements

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