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Stereoselective Synthesis of *myo*-Inositol via Ring-Closing Metathesis: A Building Block for Glycosylphosphatidylinositol (GPI) Anchor Synthesis

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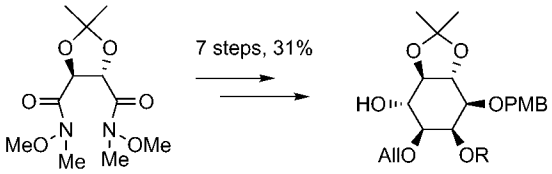
ABSTRACT



Here we report a concise stereoselective synthesis of *myo*-inositol via ring-closing metathesis. A readily available bis-Weinreb amide of D-tartrate served as a key intermediate.

The glycosylphosphatidylinositol (GPI) anchor is a post-translational modification that covalently links certain proteins to the outer leaflet of eukaryotic cell membranes (Figure 1). The phosphatidylinositol moiety is a unique feature of the GPI anchor's glycan and may be involved in clustering of GPI-anchored proteins on the cell surface.[1] GPI anchors are also prevalent in parasitic organisms such as *Trypanosoma brucei* and are major immunogenic determinants that are recognized by antigen presentation molecules in mammalian hosts.[2] Thus, GPI anchors and analogues thereof may serve as vaccine components.

Synthetic derivatives of GPI have proven to be critical tools for probing the biosynthesis, structure, and immunological properties of GPI anchors. Total syntheses of the anchor have been reported,[4] and a central theme that has emerged from these efforts is the difficulty in preparing a selectively protected *myo*-inositol building block. *myo*-Inositol or its 1,2-anhydro analogue, conduritol B, can be

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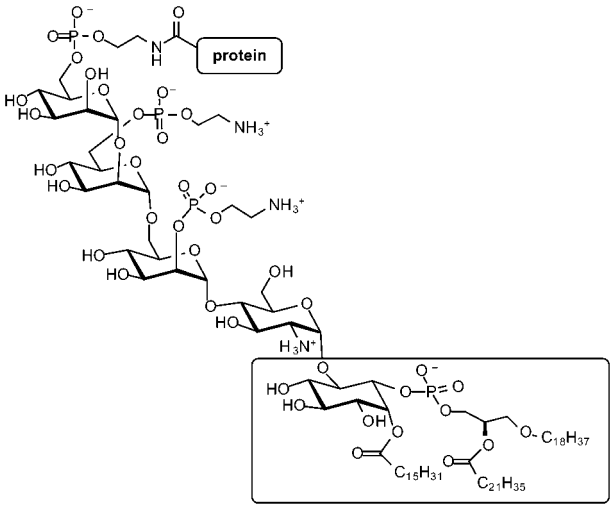
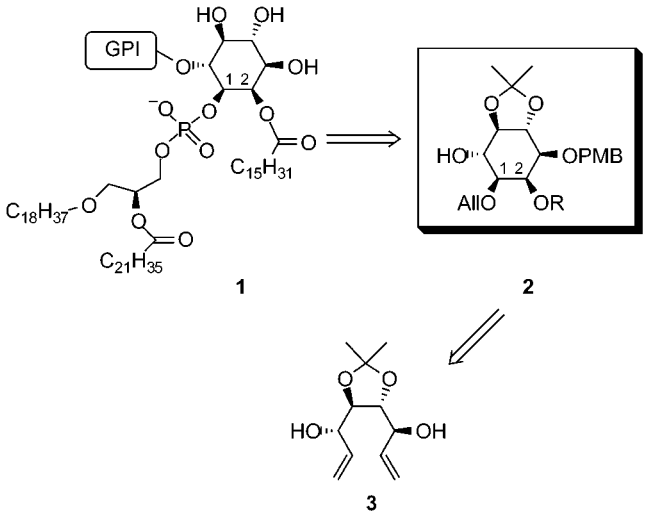


Figure 1. GPI anchor structure found on human erythrocyte acetylcholinesterase.[4] The phosphatidylinositol moiety is indicated with a box.

used as a starting material; however, their symmetry demands a resolution step,[5] and orthogonal protection of their numerous hydroxyl groups can be cumbersome.[4a,6] Alternatively, the *myo*-inositol residue can be constructed de novo from intermediates with the appropriate stereogenic centers. Ferrier rearrangement,[7] pinacol coupling,[8] and ring-closing metathesis[9] (RCM) approaches have been reported, with the latter approach involving a 1,7-diene.[10] However, Chang and coworkers were unable to form strained conduritols with the first-generation Grubb's catalyst, thus preventing the use of acetals for protection of the 4,5-diol.[10c] Herein, we describe a concise and high-yielding synthesis of differentially protected *myo*-inositol derivatives of type **2** (Scheme 1).

We targeted structure **2** as a versatile intermediate en route to compounds of type **1** (Scheme 1). We envisioned the suitably protected *myo*-inositol **2** derived from diene **3** via

Scheme 1

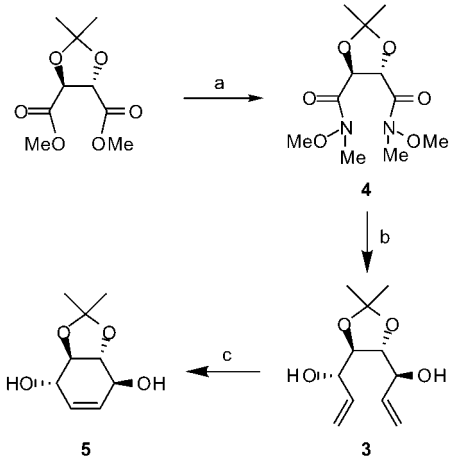


1 2 3

sequential ring-closing metathesis and dihydroxylation, followed by a short sequence of functional group manipulations. The increased reactivity of the second-generation Grubbs' catalyst[11] allows for the use of an acetal functionality at hydroxyls 4 and 5. This route permits the facile differentiation of the hydroxyl groups as they are installed. A significant advantage to this synthesis is that no resolution steps are required, and because of its C_2 symmetry before the dihydroxylation, there is no loss in yield due to the formation of diastereomers.

As shown in Scheme 2, the synthesis began with conversion of commercially available dimethyl 2,3-*O*-isopropylidene-D-tartrate to bis-Weinreb amide **4**.[12]

Scheme 2[a]



[a] Reagents: (a) CH_3NHOCH_3·HCl, $AlMe_3$, CH_2Cl_2, −10 °C, 84%; (b) (i) vinylmagnesium bromide, THF, from −78 to −5 °C; (ii) $CeCl_3$·$7H_2O$, $NaBH_4$, MeOH, −78 °C, 73%; (c) $RuCl_2CHPhPCy_3IMesH_2$ (2 mol %), CH_2Cl_2, reflux, 89%.

Addition of vinyl magnesium bromide and subsequent Luche reduction afforded the 1,7-diene **3** in 73% yield as an 11:1 mixture of diastereomers that are separable by chromatography. Ring-closing metathesis was then effected with Grubbs' second-generation catalyst[11] to afford conduritol analog **5** in 89% yield.[10d]

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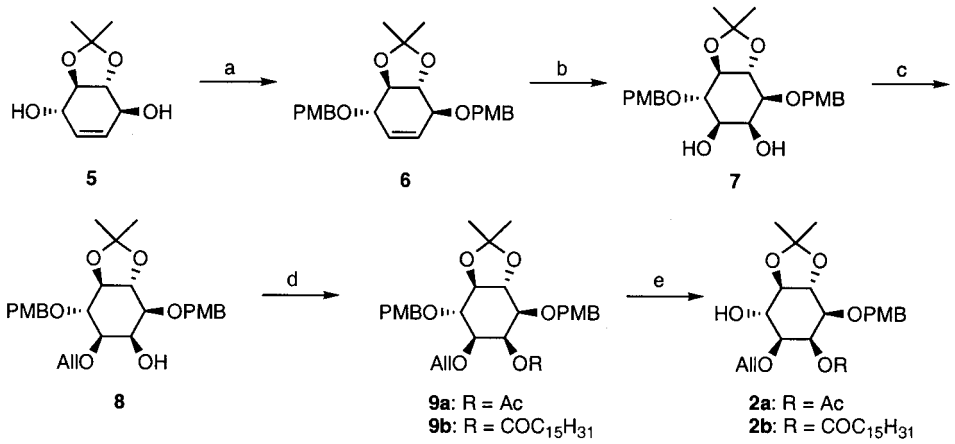
Scheme 3[a]



[a] Reagents: (a) PMBCl, $BnEt_3N^+Cl^-$, 50% KOH/H_2O, toluene, 50 °C, 90%; (b) K_2OsO_4, K_2CO_3, $K_3Fe(CN)_6$, methanesulfonamide, quinuclidine, *t*-BuOH, H_2O, 23 °C, 88%; (c) (i) Bu_2SnO, toluene, reflux; (ii) allyl bromide, $Bu_4N^+I^-$, 60 °C, toluene, 91%; (d) Ac_2O, DMAP, *i*-Pr_2NEt, CH_2Cl_2, 23 °C, 96% (gives **9a**) or palmitic acid, DCC, DMAP, THF, 23 °C, 89% (gives **9b**); (e) DDQ, CH_2Cl_2, 0 °C, 70% yield of **2a**, 60% yield of **2b**.

Simultaneous protection of the C3 and C6 hydroxyl groups as *p*-methoxybenzyl ethers afforded compound **6** (Scheme 3), which was followed by dihydroxylation to furnish the fully oxygenated *myo*-inositol intermediate **7**. Differentiation of the vicinal diol was achieved via selective C1 allylation according to the procedure of Annisuzzaman et al.[13] to produce intermediate **8** in 91% yield with greater than 40:1 regioselectivity. Subsequent acetylation of the C2 hydroxyl group provided the differentially protected *myo*-inositol **9a** in 96% yield. It should be noted that any acyl group can be installed at C2, including the naturally occurring palmitoyl group.

Finally, selective removal of the C6 *p*-methoxybenzyl ether was achieved by treatment with DDQ[14] to afford target compounds **2a** and **2b**, which are poised for elaboration of the GPI glycans from the C6 hydroxyl group.[15,16] This serendipitous reaction also proceeds in good yield in the presence of an unprotected C2 hydroxyl group. The origin of regioselectivity in this oxidative debenzylation reaction remains unclear, but the regioselectivity contributed considerably to the efficiency of the synthetic route.

In summary, we synthesized *myo*-inositol analogue **2**, which is suitable for GPI anchor synthesis, in seven steps and 31% overall yield from bis-Weinreb amide **4**. This synthesis route allows for rapid access to a conduritol B intermediate and utilizes regioselective removal of one *p*-methoxybenzyl ether in the presence of another. To our knowledge, this represents the most efficient and high-yielding approach to date and should greatly accelerate GPI anchor syntheses.

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Supporting Information Available: Full experimental procedures and spectroscopic data for all synthetic compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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