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SYNTHETIC STUDIES ON GLYCOPHOSPHATIDYLINOSITOL ANCHOR: A HIGHLY EFFICIENT SYNTHESIS OF GLYCOBIOSYL PHOSPHATIDYLINOSITOL THROUGH H-PHOSPHONATE APPROACH[1)]

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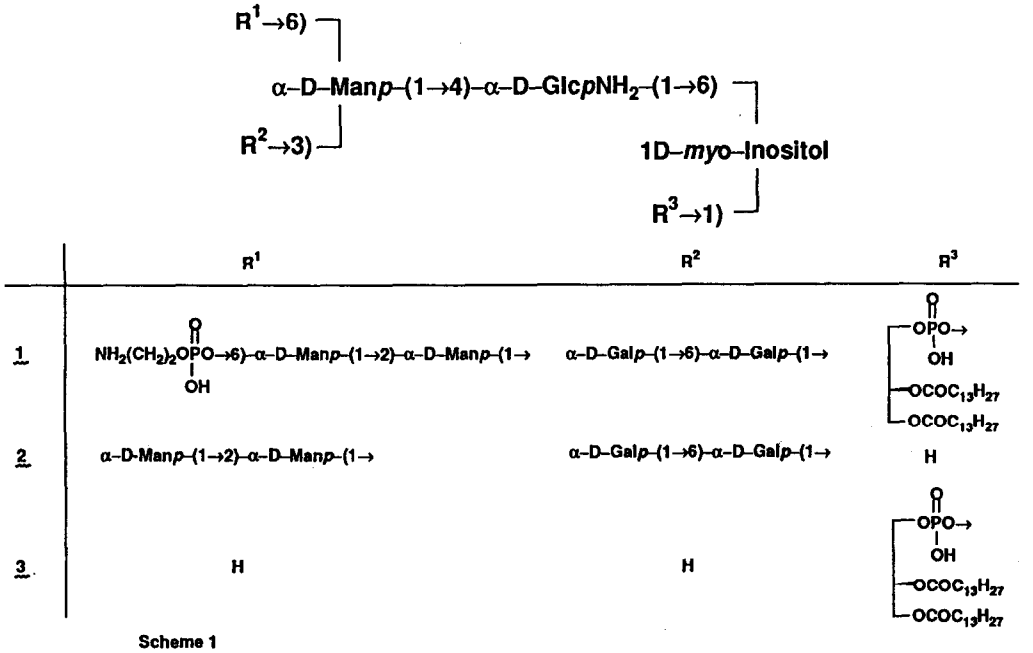
Abstract: An efficient synthetic route to the glycobiosyl phosphatidylinositol is developed by use of a H-phosphonate intermediate.

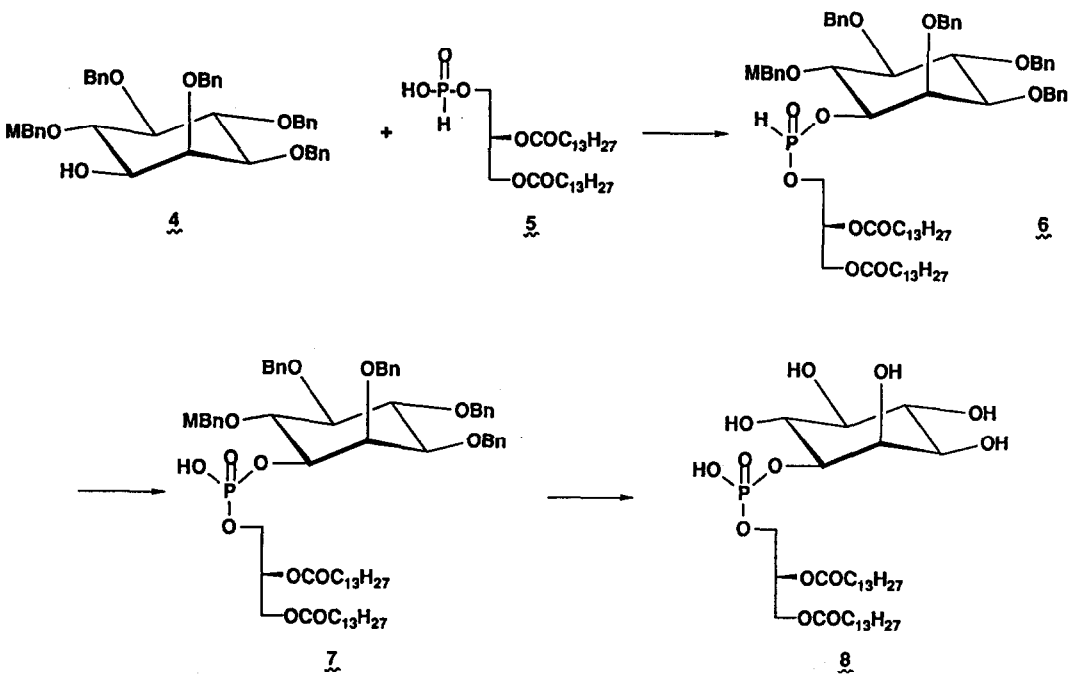
Aiming at a total synthesis of a glycophosphatidylinositol[2] (GPI) anchor **1** of the parasitic protozoan *Trypanosoma brucei*, we recently reported a stereocontrolled synthesis[3] of glycoheptaosyl core **2** of the GPI anchor **1**. As part of the project we now describe an efficient synthesis of glycobiosyl phosphatidylinositol **3**, a part structure of the GPI anchor **1**, that is proposed to play role as a second messenger for insulin action[4] as well as a signalling molecule in Qa-2 mediated T-cell activation[5].



Scheme 1

Our synthetic strategy for the target molecule **3** depends on an efficient introduction of phosphodiester function at O-1 of 1D-*myo*-inositol. This could be achieved successfully, after intensive examination of the available synthetic technologies[6], by employing H-phosphonate approach[7] that was originally developed[8] for the oligonucleotide synthesis.

First, we applied H-phosphonate approach to the synthesis of phosphatidylinositol **8**. A properly protected 1D-*myo*-inositol **4**[3] was coupled in the presence of pivaloyl chloride in pyridine with 1,2-di-O-myristoyl-3-O-H-phosphonyl-*sn*-glycerol **5**[9] that was prepared according to the method of Lindh and Stawinski[7], to give an 80% yield of a diastereomeric mixture of H-phosphonate diester **6**[9]. Oxidation of **6** with I_2 in 50:1 pyridine-water gave **7** in 71% yield as a triethylammonium salt, which was subsequently hydrogenolyzed in the presence of 20% $Pd(OH)_2$-C to afford quantitatively phosphatidylinositol **8**. The conversion of **4** into **8** was achieved in 57% overall yield in a similar efficiency observed for the different approaches[10].

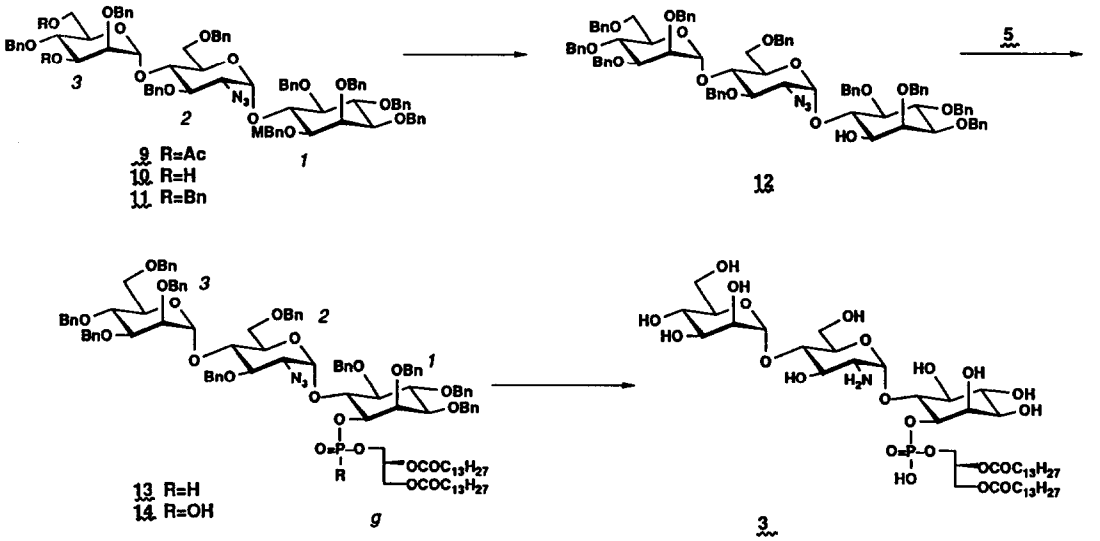


Scheme 2 (MBn = 4-MeO-Bn)

To execute the synthesis of glycobiosylphosphatidylinositol **3**, was chosen as the starting material a suitably protected glycobiosylinositol **9** that was already reported[3].

Deacetylation of **9** with NaOMe in 2:1 MeOH-THF afforded **10**[9] which was benzylated (NaH, BnBr in THF) to give a 95% yield of **11**[9]. Treatment[11] of **11** with $(NH_4)_2Ce(NO_3)_6$ in 10:1 CH_3CN-H_2O gave the alcohol **12**[9] in 79% yield. Coupling of **12** with H-phosphonate **5** in the presence of pivaloyl chloride in pyridine afforded a 79% yield of the desired H-phosphonate diester **13**[9] as a diastereomeric mixture, that was then oxidized with I_2 to afford an 89% yield of the phosphate diester **14**[9]. It is to be noted that in our hands all the other phosphorylation methods[10] by use of either phosphodiester or phosphite chemistry for the conversion of **12** into **14** afforded

significantly inferior results. Finally hydrogenolysis of **14** in the presence of 20% $Pd(OH)_2$-C in 6:4:3 $CHCl_3$-H_2O-MeOH and purification of the product by Sephadex LH-20 in 9:7:2 $CHCl_3$-MeOH-H_2O gave **3**[9] in 51% yield.



Scheme 3

In summary, an efficient conversion of a key glycobiosylinositol derivative 9 into 3 was achieved in 6 steps in 27% overall yield. Facile and practical synthesis of glycobiosyl phosphatidylinositol 3 described above should be of significant importance from the view point of elucidation of molecular mechanisms for the possible biological functions[4,5] proposed for GPI anchors.

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Reference and Notes

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9 All new compounds were characterized by TLC and NMR as well as by combustion analysis. Physical data for key compounds are given below. Values of $[\alpha]_D$ and $\delta_{H,C,P}$ were recorded for solutions in $CHCl_3$ and $CDCl_3$, respectively, at 23°±3°, unless noted otherwise. **4**: readily obtainable from corresponding 1-O-(1S)-(-)-camphanoyl derivative[3] (NaOH in 7:3 MeOH-THF, 97%), $[\alpha]_D$ +12.1° (c 0.7); δ_H 4.024 (d, 2.4 Hz, H-2), 3.784 (OMe). **5**: $[\alpha]_D$ +4.6° (c 0.6, 9:1 MeOH-$CHCl_3$); δ_H (9:1 $CDCl_3$-CD_3OD) 6.696 (d, 629 Hz, PH), 5.215 (m, H-2), 4.388 (dd, 2.8 and 12.2 Hz, H-1), 4.178 (dd, 6.7 and 11.9 Hz, H-1'), 3.903 (m, H-3 and 3'); δ_P (9:1 $CDCl_3$-CD_3OD) 6.849 (d, 631 Hz). **6**: δ_H 3.788 and 3.787 (5:4, two OMe); δ_P 9.788 (dqr, 727 and 8.8 Hz), 8.539 (dqr, 721 and 8.8 Hz). **7**: $[\alpha]_D$ -10.0° (c 1.5); δ_H 5.187 (m, 2^g), 3.741 (s, OMe), 0.877 (t, 7.1 Hz, $2CH_3$); δ_P -0.775. **8**: $[\alpha]_D$ +13.4° (c 0.4, 5:1 $CHCl_3$-MeOH); δ_H ($DMSOd_6$) 5.081 (m, 2^g), 4.278 (dd, 12.1 and 2.9 Hz, 1^g), 4.077 (dd, 11.9 and 7.0 Hz, 1^g); δ_P ($DMSOd_6$) 1.868. **10**: $[\alpha]_D$ +54.3° (c 5.6); δ_H 5.611 (d, 3.7 Hz, 1^2), 5.287 (d, 1.5 Hz, 1^3), 3.655 (OMe). **11**: $[\alpha]_D$ +39.6° (c 0.8); δ_H 5.631 (d, 3.6 Hz, 1^2), 5.343 (d, 2.1 Hz, 1^3), 3.556 (OMe). **12**: $[\alpha]_D$ +36.8° (c 0.6); δ_H 5.403 (d, 3.7 Hz, 1^2), 5.226 (d, 1.8 Hz, 1^3). **13**: δ_H 5.599 (d, 3.7 Hz, 1^2), 5.284 and 5.261 (0.6H and 0.4H, d, 2.0 Hz, 1^3), 5.189 (m, 2^g); δ_P 9.184 (dqr, 719 and 8.8 Hz), 8.358 (dqr, 723 and 9.8 Hz). **14**: $[\alpha]_D$ +19.4° (c 2.1); δ_H 5.423 (d, 3.7 Hz, 1^2), 5.205 (m, 2^g), 5.196 (d, 1.6 Hz, 1^3); δ_p -1.853. **3**: R_F 0.43 in 9:7:2 $CHCl_3$-MeOH-4*N*NH_4OH); $[\alpha]_D$ +63.5° (9:7:2 $CHCl_3$-MeOH-H_2O); δ_H (49:1 $DMSOd_6$-D_2O, 60°) 5.270 (d, 3.4 Hz, 1^2), 5.231 (d, 1.5 Hz, 1^3), 5.094 (m, 2^g), 4.309 (dd, 3.1 and 11.9 Hz, 1^g), 4.098 (dd, 7.3 and 11.9 Hz, $1'^g$), 4.046 (t, 2.4 Hz, 2^l), 2.814 (dd, 3.1 and 10.4 Hz, 2^2); δ_P (49:1 $DMSOd_6$-D_2O) 0.284.

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