THE CHEMICAL SYNTHESES OF BIO-ACTIVE GPI ANCHORS FROM *TRYPANOSOMA CRUZI*: EXPLORATION OF ESTER AND ACETAL TYPE PROTECTING GROUPS

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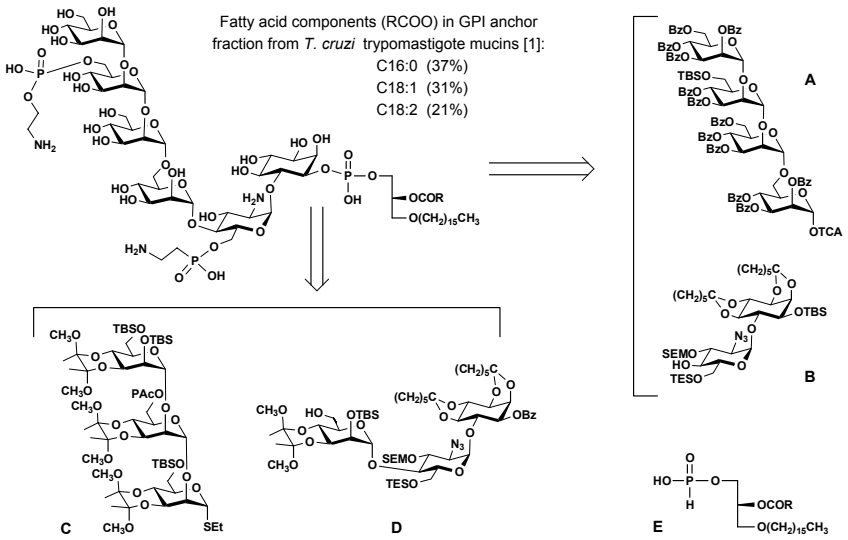
Glycosylphosphatidylinositols (GPIs) are a class of natural glycosylphospholipids that anchor the *C*-termini of proteins, glycoproteins and phosphoglycans to the membrane of eukaryotic cells. The discovered role of GPIs as mediators of regulatory processes makes the chemical preparation of the compounds and their analogues of great interest. It has been shown that *T. cruzi* trypomastigote mucin GPIs are potent inducers of TNF-α, IL-12 and nitric oxide in macrophages.[1] The activity was allegedly associated with the presence of unsaturated fatty acid (UFA) esters in the phospholipid moiety or/and galactose branches (non-stoichiometric, not shown) along the glycan core. Two *T. cruzi* GPIs bearing oleic (C18:1) or linoleic (C18:2) esters were prepared following novel synthetic strategy and using permanent *O,N*-protecting groups compatible with the presence of the double bonds. Thus, the **A**+**B** coupling (→ glycan-inositol block) followed by consecutive introduction of the phosphonate and phosphate moieties gave the corresponding protected GPIs containing *N*-Boc and *O*-benzoyl/acetal protections. Mild basic treatment (with advantageous cleavage of the benzoates in the presence of the UFA esters) followed by acid hydrolysis gave the targeted GPI anchors. Alternatively (the **C**+**D** condensation), the acetals/diacetals/TBS ethers were exploited for *O*-protection thus securing the one-step final *O,N*-deprotection performed with aqueous TFA. In biological tests, the synthetic GPIs revealed the activity identical to the one found in naturally occurred GPIs.



[1] Almeida, I.C., Camargo, M.M., Procopio, D.O., Silva, L.S., Mehlert, A., Travassos, L.R., Gazzinelli, R.T. and Ferguson, M.A.J. *EMBO J.*, 2000, **19**, 1476-1485