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A Suzuki–Miyaura coupling mediated deprotection as key to the synthesis of a fully lipidated malarial GPI disaccharide†

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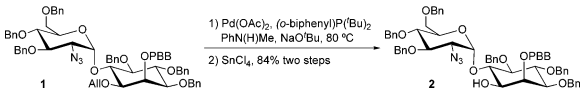
Ligandless palladium-catalyzed Suzuki–Miyaura coupling converted an inert *p*-bromobenzyl ether to a DDQ-labile *p*-(3,4-dimethoxyphenyl) benzyl ether in the presence of azide functionality and this strategy serves as a key step for the convergent synthesis of a fully lipidated malaria GPI disaccharide.

Glycosylphosphatidylinositols (GPIs) are a class of glycolipids that link proteins to cell membranes. In addition to this simple anchoring function GPIs trigger various biological events inside the cell.[1] We have recently identified a GPI as the dominant pro-inflammatory toxin of *Plasmodium falciparum* origin.[2] A synthetic GPI glycan conjugated to a carrier protein served as an effective anti-toxin malaria vaccine in a rodent model. The total synthesis of defined malarial GPI is essential for detailed investigations into the role of GPIs in malarial pathogenesis and signaling mechanisms.

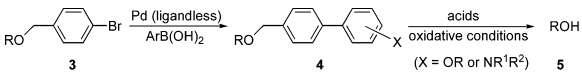
Diligent work on the structural elucidation of the malarial GPI by several groups[3] has yielded a proposed consensus structure (Fig. 1) although the exact nature of the lipid portions remains elusive. To establish the exact structure of the malarial GPI, the synthesis of a series of GPI glycans containing a variety of lipids will be required. To introduce a variety of lipid structures on inositol at the final stage of the synthesis, the assembly of a hexasaccharide glycan backbone with three orthogonal protecting groups is essential. No such approach has been reported.[4] Herein, we describe the realization of a synthetic strategy to access lipidated GPIs and its application to the transformation of key intermediate **1** to a fully lipidated malarial GPI disaccharide.

In a previous synthesis[5] we have demonstrated that triisopropylsilyl (TIPS) and allyl groups serve as reliable protecting groups for the two phosphorylation sites in the penultimate mannose and on inositol. One additional protecting group on the C2 hydroxyl on inositol will be required. Conditions used during the assembly of the glycan demand the exclusion of base-sensitive esters, acid-sensitive ethers, and silyl groups. Mindful of these restrictions, we envisioned that the acid- and base-stable *p*-bromobenzyl (PBB) group would be suitable. The PBB group can be readily removed by conversion to an acid-labile *p*-aminobenzyl group *via* a Pd-mediated amination reaction.[6] Disaccharide **1**[7] served as target in evaluating this approach on the α-linked glucosamine-inositol core of the malarial GPI. The attempted removal of the PBB group by catalytic amination[6] failed to afford the desired disaccharide. Instead, the allyl group was removed cleanly to give disaccharide **2** (eqn. (1)). The azide group in **1** most likely poisoned the phosphine ligand essential for the Pd-catalyzed amination, and the harsh basic conditions isomerized the allyl group, which was readily removed by $SnCl_4$.



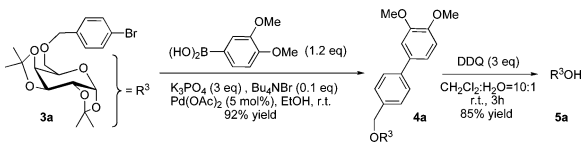
(1)

Faced with the challenge of finding a suitable protecting group ensemble we designed another avenue to remove the PBB group. Substituted benzyl ethers, such as *p*-methoxybenzyl (PMB) ether, are often more labile toward acids and oxidants than benzyl ether.[8] We envisioned that these reactivities would be retained through π-conjugation in a hetero-substituted *para*-arylbenzyl ether. Surprisingly, no such benzyl ether had been utilized previously.[9] PBB ethers should be converted to the more labile, substituted *para*-arylbenzyl ethers *via* a Pd-catalyzed Suzuki–Miyaura coupling without using phosphine ligands and be subsequently removed by acids or oxidants (eqn. (2)). This ligandless approach would circumvent any problems brought about by azide poisoning of phosphine ligands.



(2)

Among the host of procedures for the ligandless Suzuki–Miyaura coupling,[10] the mild conditions reported by Gong *et al.*,[10d] involving catalytic amounts of Pd(II) acetate and tetrabutyl ammonium bromide in ethanol open to air was particularly appealing. After the original procedure did not yield reproducible results in our hands, the exclusion of air from the reaction media resulted in complete conversion and high coupling yields. A screen of different coupling partners found 3,4-dimethoxyboronic acid to be ideal since the resulting *p*-(3,4-dimethoxyphenyl)benzyl (DMPBn) ether could be cleaved by DDQ.[11] Thus, PBB-protected galactose **3a** was transformed to DMPBn-protected **4a** *via* the ligandless Suzuki–Miyaura coupling in 92% yield. Treatment of **4a** with DDQ yielded deprotected **5a** (85%, eqn. (3)).



(3)

With the optimized protocol in hand, the compatibility of the newly developed strategy for the removal of the PBB group was examined with other commonly used modes of protection using substrates **3b–3e** (Table 1). The ligandless coupling approach worked very well with substrates containing azides, silyl ethers, allyl groups, esters and glycals that remained intact during the coupling and DDQ deprotection step. The coupling yields ranged from 63% to 93% and DDQ deprotection was high yielding in all cases.

While examining the reactivity of the DMPBn ether toward oxidants and acids, we observed that DMPBn is as labile as PMB when treated with DDQ, however, much more resistant to acids. This finding suggested that DMPBn alone could also serve as an effective protecting group in organic transformations. Thus, DMPBnBr **6** was synthesized from *p*-bromobenzyl alcohol (eqn.

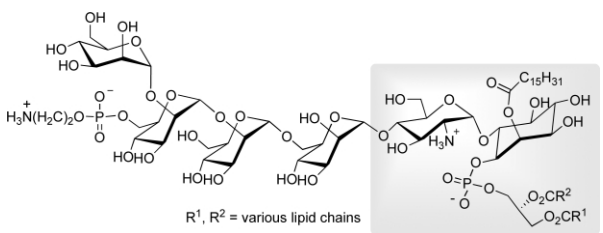


Fig. 1 Proposed GPI structure of *P. falciparum*.

† Electronic supplementary information (ESI) available: General information and procedures (S1–S13) and copies of NMR spectra (S14–S54). See http://www.rsc.org/suppdata/cc/b4/b407324j/

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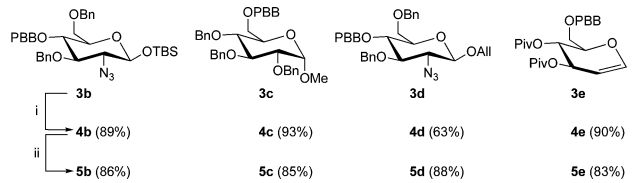
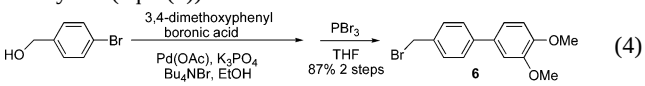


Table 1 Functional group compatibility for PBB removal[a]

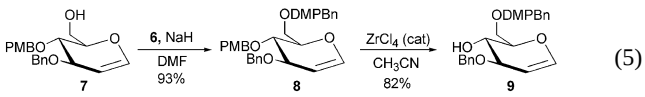
3b	3c	3d	3e
4b (89%)	**4c** (93%)	**4d** (63%)	**4e** (90%)
5b (86%)	**5c** (85%)	**5d** (88%)	**5e** (83%)

[a] Reagents and conditions: (i) 3,4-dimethoxyphenylboronic acid (1.2 equiv.), $Pd(OAc)_2$ (0.05 equiv.), Bu_4NBr (0.1 equiv.), K_3PO_4 (3 equiv.), reagent grade ethanol, r.t. 2–3 h. (ii) DDQ (3 equiv.), CH_2Cl_2:H_2O (10:1), r.t. 3h. Number in parentheses represents isolated yield.

(4)). The C6 hydroxyl group of glycal **7** was readily protected with DMPBn group and the C-4 hydroxyl group in **8** was liberated selectively from the PMB group using catalytic amounts of $ZrCl_4$ in 82% yield (eqn. (5)).[12]

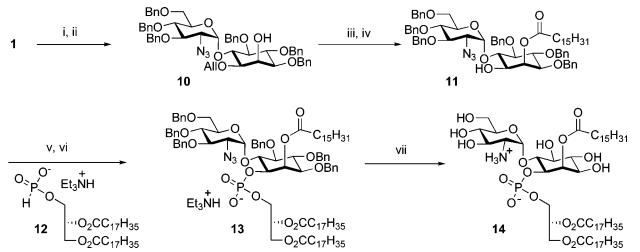


(4)



(5)

Following the methodological advances, we applied the newly developed protecting group strategy to the functionalization of disaccharide **1**. Coupling of **1** with 3,4-dimethoxyphenylboronic acid using the ligandless protocol readily converted the PBB group to DMPBn, that was readily cleaved by DDQ to afford **10** in 65% yield over 2 steps. Palmitoylation followed by deallylation furnished **11** without acyl migration. Successive phosphorylation and oxidation fashioned fully protected disaccharide **13**. Global deprotection with Pearlman's catalyst gave rise to fully lipidated disaccharide **14** in quantitative yield.[13]



Scheme 1 Synthesis of fully lipidated disaccharide **14**. (i) 3,4-dimethoxyphenylboronic acid, 5 mol% $Pd(OAc)_2$, 10 mol% Bu_4NBr, K_3PO_4, EtOH; (ii) DDQ, CH_2Cl_2:H_2O (10:1), 65% 2 steps; (iii) $C_{15}H_{31}COOH$, DMAP, DCC, 87%; (iv) $PdCl_2$, NaOAc, HOAc, H_2O, 69%; (v) **12**, PivCl, pyridine; (vi) I_2 in pyridine/H_2O, 90% 2 steps; (vii) $Pd(OH)_2$, H_2, $CHCl_3$:MeOH:H_2O (3:3:1), quant.

In conclusion, we achieved the first synthesis of a fully lipidated malarial GPI disaccharide based on a new protecting group strategy involving substituted benzyl ethers. We demonstrated a new method to utilize *p*-bromobenzyl ethers as protecting groups. The chemically stable PBB group was effectively converted to a DDQ-labile *p*-(3,4-dimethoxyphenyl)benzyl ether using a ligandless Pd-catalyzed Suzuki–Miyaura coupling reaction. This protecting group served as a key for the access to the lipidated malarial GPI disaccharide. This study reports for the first time the use of *p*-(hetero-substituted phenyl)benzyl ethers as effective protection for hydroxyl groups. The reactivity of such groups can be tuned by the substitution patterns on the aryl rings and should find wide application in the synthesis of complex molecules beyond carbohydrates.

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