Synthesis of hydrolytically stable porphyrin *C*- and *S*-glycoconjugates in high yields†

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Two *C*-glucosyl porphyrins are prepared using Ramberg–Backlund and Lindsey methods for the key conversions, and thiosugars are shown to react with perfluorophenylporphyrins.

Photofrin®, a mixture of hematoporphyrin oligomers, is currently used clinically for the photodynamic therapy (PDT) of cancers, but suffers from a variety of problems including solubility and dosing.[1] Because of their potential selective binding to various cell types, porphyrins appended with a variety of saccharides have been examined as possible agents for PDT.[1,2] Most recently, sugar-specific binding to rat hepatoma cells by porphyrin glycoconjugates has been described.[2] Their efficacy as antibiotics and anti-viral agents is also under intense investigation.[1] Since metalloporphyrins are well-established catalysts, the attachment of sugars to effect regio- and stereo-selective oxidations has also been examined, albeit with limited success.[3] Additionally, there are several requirements for the successful commercialization of any of these adducts: (a) effective synthesis in high yields, (b) stable products, in this case to hydrolysis, and (c) highly pure compounds.

It is interesting that with few exceptions,[4–6] the glycoconjugate has been oxygen linked *via* a glycosidic bond to a phenolic aryl porphyrin. When the syntheses of these O-linked materials are examined, one finds that disappointingly low yields are reported, considering that the Lindsey porphyrin synthesis yields are typically 45–65%.[7] We believe that one problem may be that the frequently used *O*-glycosyloxybenzaldehyde starting materials, when subjected to the Lindsey porphyrin synthesis using BF$_3$ catalysis, can undergo a competing and yield-reducing Suzuki *O* to *C*-glycoside rearrangement.[8] Additionally, a perceived problem with the *O*-glycosides is the inherent possibility for glycosyl cleavage by acids, and in biological systems by glycohydrolases. We wish to describe our preliminary results, which provide possible solutions to both the issues of poor yields and hydrolytic instability, namely the preparation of *C*- and *S*-glycosylated aryl porphyrins in high yields. Both yield and stability are crucial factors for the successful incorporation of sugar moieties into porphyrin combinatorial libraries, since the linkage must be stable both during the formation, subsequent reactions, and in the presence of a variety of functional groups.

For the *C*-glycoside series, we chose to exploit earlier work from our laboratory where the Ramberg–Backlund synthesis is used to link sugars to aglycones.[9,10] Thus, after screening several alternative functional equivalents of *p*-bromomethyl-benzaldehyde, we settled on α,α′-dibromo-*p*-xylene as an inexpensive starting material. This was condensed with 1-thio-β-D-glucose tetraacetate[11] to afford thioglucoside **1**. Then conversion to the silylated material **2** was accomplished by treatment of **1** with *tert*-butyldimethylsilanol in the presence of silver triflate and 2,6-di-*tert*-butylpyridine.[12] The replacement

of the acetyl groups with benzyl ethers to obtain **3** was achieved by deprotection of **2** with sodium methoxide, followed by benzylation. The sulfide **3** was oxidized to the sulfone **4** with monoperoxyphthalic acid (MMPP). The resulting sulfone was employed in the Ramberg–Bäcklund synthesis of the *exo*-glucal **5** under Chan's conditions.[13] The two isomers (*Z*)-**5** and (*E*)-**5** in the ratio 8:2 were identified by NOE measurements, which showed an effect between H-1 and H-3 in the case of the *E*-isomer. In some cases the intermediate α-bromosulfone **6** was isolated from the reaction mixture and then converted to the *exo*-glucal **5** by treatment with base. The hydrogenation of **5** with palladium 5% on alumina afforded the β-*C*-glucoside **7**, identified by the coupling constant *J* = 9.2 Hz, indicating an anti-diaxial configuration of the anomeric H-2 with respect to H-3. The cleavage of the silyl ether **7**, followed by Swern[14] oxidation gave the aldehyde **9**, which was utilized in the synthesis of the porphyrins **10** and **11** in 15 and 53% yields respectively, under Lindsey conditions.[7] The materials obtained showed the expected spectroscopic data. The hydrogenolysis of the benzylic protecting groups yielded the porphyrins **12** and **13**, without reduction of the porphyrin. *S*-Glycosides were chosen as worthy conjugates because they are considered to be good mimics of *O*-glycosides with enhanced stability toward enzymatic hydrolysis.[15]

The second reaction sequence begins with 5,10,15,20-tetra-(perfluorophenyl)porphyrin which can be routinely made in gram quantities in high yields by the Lindsey procedure.[7] The reactivity of the *para*-fluoro group toward a large variety of nucleophilic substitution reactions has been well established.[4,16] The tetrakis(thiogalactosyl) and tetrakis(thioglucosyl) derivatives of this fluorinated porphyrin are formed in > 85 and 90% yields, respectively, by modifications of previously described procedures.[16] Specifically, the porphyrin is dissolved in amine-free DMF, five equiv. of the sodium salt of the thiosugar added, and the mixture stirred at rt for 4 h. Purification is accomplished on silica-gel using an ethanol–ethyl acetate gradient as eluent.

DNA photocleavage assays are widely used to evaluate the photoreactivity of porphyrin compounds, though DNA is not the primary site of Photofrin activity.[1,5,6] Thus we used standard plasmid photocleavage assays to evaluate the photoreactivity and compare these results with those for other porphyrins. The conditions used to evaluate the photodamage to plasmid DNA caused by porphyrin compounds varies, but our analysis (see

Table 1

Compound	Partition coeff. octanol–water	DNA photocleavage
5-glu-triPP **12**	68	Fair
Tetra glu PP **13**	30	Poor
Tetra thio glu F4PP	50	Poor
Tetra thio gal F4PP	38	Fair
DiMePy + MeOHP[a]	7	Excellent

[a] Ref. 17.
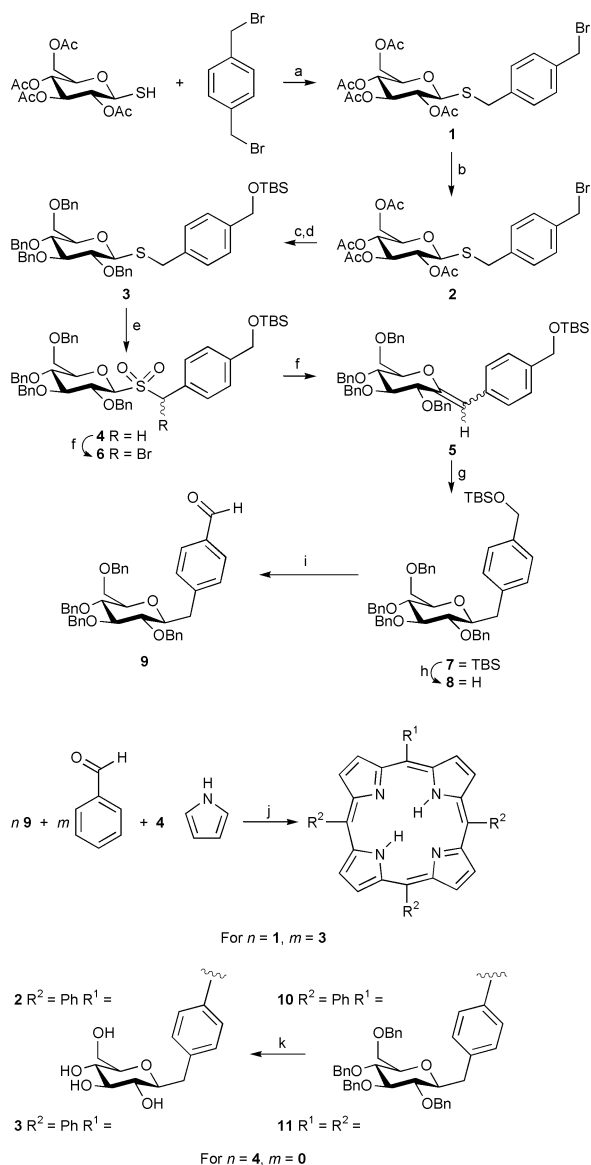
Scheme 1 **a**, NaH, THF, rt, 2 h, 90%; **b**, TBDMSOH, Ag(OTf), 2,6-di-*tert*-butylpyridine, CH$_2$Cl$_2$, rt, 3 h, 60%; **c**, MeONa, MeOH, rt, 3 h; **d**, NaH, BnBr, Bu$_4$N$^+$I$^-$, THF–DMF, rt, 8 h, 80% for 2 steps; **e**, MMPP, THF–EtOH–H$_2$O, 60 °C, 2 h, 87%; **f**, CBr$_2$F$_2$, KOH 25% on alumina, CH$_2$Cl$_2$–*t*-BuOH, 0 °C to rt, 3 h, 88%; **g**, H$_2$, Pd 5% on alumina, EtOAc, rt, 12 h, 95%; **h**, Bu$_4$N$^+$F$^-$, THF, rt, 2 h, 98%; **i**, Oxalyl chloride, DMSO, CH$_2$Cl$_2$, −78 °C, then Et$_3$N, −78 °C to rt, 1.5 h, 85%; **j**, BF$_3$·OEt$_2$, NaCl, rt, 5 h, then DDQ, rt, 30 min, 15% for **10**, 53% for **11**; **k**, H$_2$, Pd 10% on carbon, EtOAc–MeOH, rt, 16 h, 98%.

Table 1 indicates the compounds reported herein exhibit poor photoreactivity which is consistent with other glycosylated porphyrins.[1,5,6] The amphipathic character of the macrocycle derivative has been shown to correlate to cell toxicity *in vitro*,[1] so the partition coefficients are reported. To date, for this class of compounds, the activity is much poorer than the 5,10-bis(4-methylpyridinium)-15-(4-methylphenyl)-20-(4-hydroxy-phenyl)porphyrin (DiMePy$^+$MeOHP) found by combinatorial methods,[17] and for some other tetraphenylporphyrin derivatives.[1]

In conclusion, both the C and S linked glycoporphyrins can be synthesized in high yields exceeding 50% based on starting aldehydes using more efficient synthetic strategies. These compounds are stable to hydrolysis and show some photo-

activity. Despite significant efforts by a large number of groups, there are few effective photodynamic therapy (PDT) agents, thus there remains a need to further develop the chemistry and the structure–activity relationships of this class of compounds. In contrast to the present clinical use of Photofrin® for the PDT of cancers, it may be found that different porphyrinic compounds are needed to more effectively treat different cancerous tissues, or for other therapeutic uses.

Notes and references

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