Synthesis of Novel Porphyrin–Uridine Carbon–Carbon Conjugates

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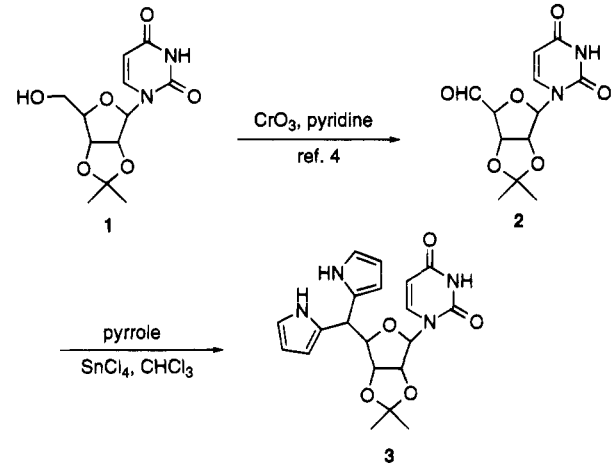
Linking porphyrinyl cores and related macrocycles to biomolecules by means of covalent bonds often results in formation of stable hybrid entities which display a number of useful functions.[1,2] In this context, synthetic nucleobase and nucleoside conjugates[2] have emerged as a quite promising class of molecules with functions, having applications in areas such as molecular recognition and transport,[2a,b] energy- and electron-transfer processes,[2c,d] antiviral and anticancer therapies,[2e-h] and inhibition of gene expression.[2i,j]

Recently, we have embarked upon a research program designed to access a series of structurally defined glycoconjugated porphyrins, wherein the carbohydrate moieties are anchored to the tetrapyrrole macrocycle by means of robust carbon–carbon bonds.[3] It was found that acid-catalyzed coupling of cyclic and acyclic sugar aldehydes with pyrrole or suitable dipyrrylmethane units results in rapid formation of *C-meso*-bonded porphyrinyl hybrids equipped with a variety of sugar residues. The success of this work has led us to exploit similar chemistry to create carbon–carbon linked nucleoside–porphyrin conjugates, which represent a little studied group of porphyrinyl nucleoside conjugates.[2g] We now wish to report successful preparation of two novel lipophilic di- and tetrasubstituted uridinyl porphyrins, **4** and **5**, by exploiting *C*-glycosylated dipyrrylmethane **3** as a common building block. We also wish to report the preparation of the fully deprotected counterparts **6** and **7**, showing amphiphilic and hydrophilic character, respectively.

Our syntheses (Scheme 1) began with the coupling of 2 equiv of pyrrole to 1 equiv of uridine carboxaldehyde **2**, which was in turn prepared by conventional pyridinium chromate oxidation of known 2′,3′-*O*-isopropylideneuridine (**1**).[4] In the event ($SnCl_4$ in 20 mM $CHCl_3$), key dinuclear intermediate **3** was obtained in a reasonable 33% yield.[5] With a view toward synthesizing the 5,15-bis-uridinyl derivative **4**, we have first examined the direct macrocyclization of **3** with 4-fluorobenzaldehyde (Scheme 2). Paralleling our recently optimized cyclization protocol,[3] using 1 equiv of BF_3 etherate in 5 mM dichloromethane followed by DDQ oxidation, D_2-symmetric porphyrin **4** was obtained as a homogeneous red solid in 15% yield after silica gel chromatography.

Scheme 1



For 5,10,15,20-tetrakisuridinylporphyrin **5**, coupling of the same precursor **3** to uridine aldehyde **2** was next planned. In spite of the steric overload of the tetrapyrrole periphery by four large nucleoside substituents, we were pleased to observe that application of the same protocol as that used for the aryl-substituted compound **4** ensured expeditious preparation of D_4 symmetric porphyrin **5** in an acceptable 10% yield after two silica gel chromatographic purifications.

Cleavage of all the acetonide protections within **4** and **5** was quickly attained upon exposure to aqueous trifluoroacetic acid at ambient temperature. There was obtained, after ammonia neutralization, unprotected porphyrins **6** and **7** in nearly quantitative yield. While porphyrin **7** showed high water solubility at 25 °C (up to 0.4×10^{-3} M), diaryl-substituted derivative **6** displayed reduced solubility in water, but ample solubility (up to 0.54×10^{-3} M) in a 80:20 water–methanol mixture.

The porphyrins **4-7** were characterized using various spectral analyses, including high-resolution mass, UV–vis, CD, and ^1H NMR spectroscopies. Low-resolution FAB MS of **4-7** gave molecular weights which are those expected of the corresponding formulas, while high-resolution measurements gave rise to exact $(M + 1)^+$ masses. The electronic spectra of protected compounds **4** and **5** were similar to each other with strong Soret bands at 412–416 nm, accompanied by four less intense Q bands in the region 515–650 nm. The UV–vis spectra of the corresponding deprotected counterparts **6** and **7** showed different profiles with Soret bands of reduced intensity associated with only two Q bands. The solutions of **4-7** were CD active at room temperature showing induced Cotton effects at the Soret band region indicating significant transmittal of the sugar chirality to the

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(5) Preliminary attempts to optimize the coupling protocol using a recent methodology gave substantially similar results; see: Lee, C.-H.; Lindsey, J. S. *Tetrahedron* **1994**, *50*, 11427.

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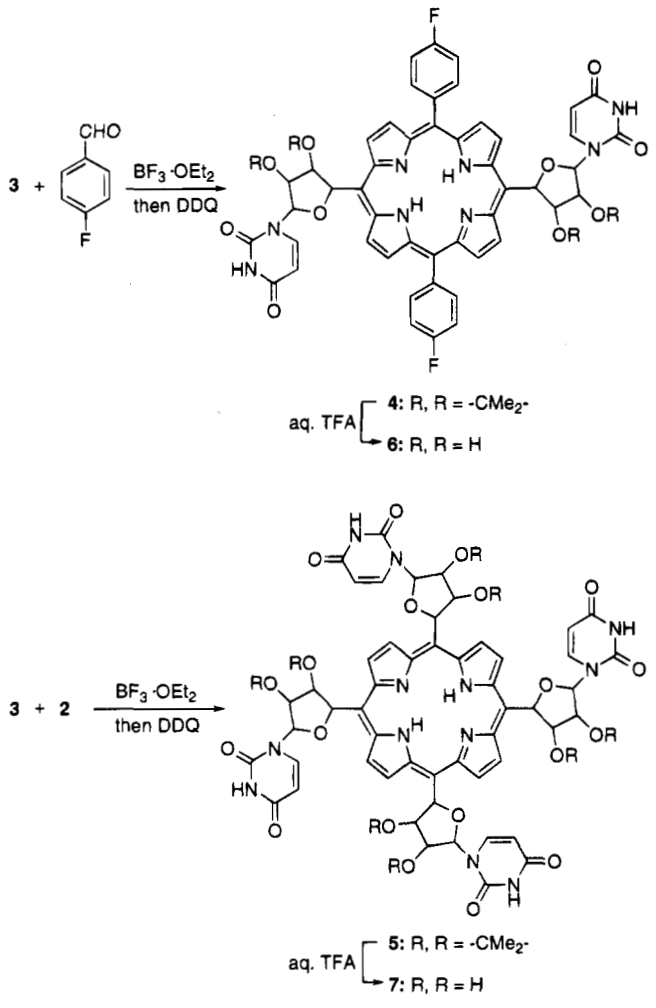
Scheme 2



porphyrin chromophore. Interestingly, while CD profiles of **5-7** in methanol showed marginal concentration dependence, dramatic changes were observed for **4** when the spectra were recorded in increasingly concentrated chloroform solutions (see Figure 2 in the supporting information). This result can be attributed to favorable self-aggregation of the individual porphyrins, likely assisted by cooperative $\pi-\pi$ staking and internucleobase H-bonding.[6] The ^{1}H NMR spectra of **4** and **6** reflect the D_2 symmetry of the molecules resulting in two doublets each integrating to four protons attributed to the β-pyrrolic resonances and one resonance system corresponding to the two equivalent nucleoside moieties. On the contrary, reflecting their D_4 symmetry, porphyrins **5** and **7** showed only a singlet for the eight β-pyrrole protons and one resonance system for the four equivalent sugar appendages.

To conclude, what we have presented herein is a remarkably short entry to an unprecedented progeny of porphyrinyl hybrids embodying integral nucleosidic residues connected to the porphyrin *meso*-positions through only one robust carbon–carbon bond. This linking mode brings the two functional components of the molecule in close vicinity, paving the way for future application in the chiral recognition and DNA binding studies. We also intend to apply this methodology to preparation of porphyrinyl conjugates carrying complementary peripheral nucleosides (*e.g.*, thymidine–adenosine and cytidine–guanosine pairs) to assemble various hydrogen bonded noncovalent ensembles.

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Supporting Information Available: Experimental details and compound characterization data; copies of UV–vis and CD spectra of **4-7** (Figures 1–8) (10 pages).

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