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Synthesis and Transformation of Pyrrole *C*-Glycoconjugates

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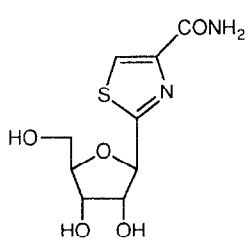
Abstract: *Enantiomerically pure open chain α-pyrrylalditols* ***2***, ***3***, ***5***, *and* ***7*** *and dinuclear dipyrrylmethanes* ***8-10*** *bearing chiral alditolyl bridges have been synthesized by direct coupling of glyceraldehyde* ***1***, *arabinose* ***4***, *and glucose* ***6*** *with pyrrole metal reagents based on magnesium-titanium^{IV} or magnesium-cerium^{III} blends. The mononuclear and dinuclear compounds were then exploited as precursors for the preparation of either cyclic C-nucleoside analogs* ***11-14***, *or the sugar porphyrin* ***16***.

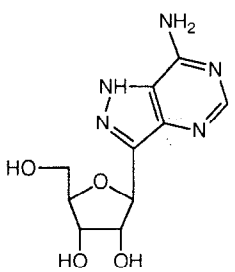
INTRODUCTION

C-glyconjugates of certain nitrogen heterocycles such as the compounds below (Chart 1) form an important subclass of nucleosides which display strong and varied biological activities;[1] as a consequence, there has recently been considerable interest in the preparation of carbon-linked nucleoside congeners and analogs including acyclonucleosides, for testing and structure-activity studies.[2]

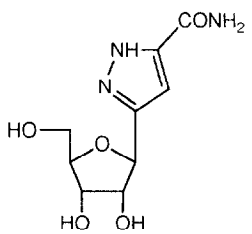
Chart 1



Thiazofurin



Formycin



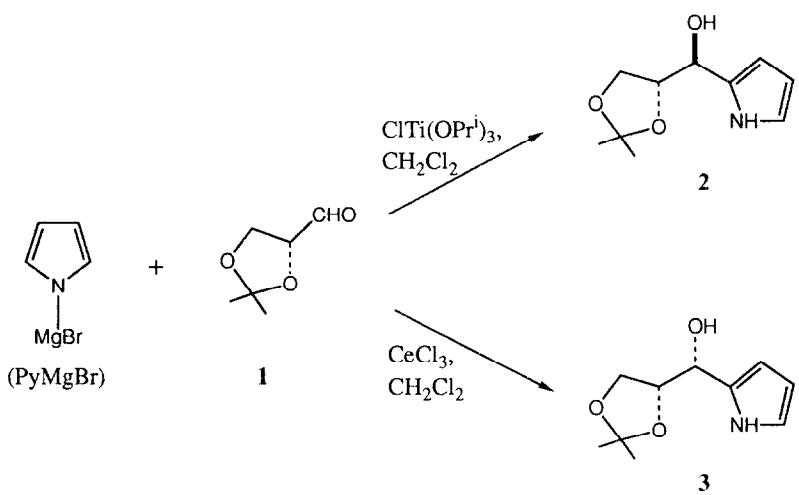
Pyrazomycin

In the present work we studied the direct *C*-heteroarylation of acyclic and cyclic sugars by means of pyrrole[3] as a model nitrogen heterocycle assisted by suitable metal promoters, including magnesium-titanium^{IV} and magnesium-cerium^{III} blends. This procedure yielded a series of mononuclear and dinuclear α-pyrrylalditol derivatives, in which the arylation mode and product stereochemistry depend on the nature of the starting sugar and the involved metal species. Transformation of the enantiomerically pure pyrrylalditols into furanosidic and pyranosidic pyrrole *C*-nucleosides and *C*-glycoconjugated porphyrins form a further subject of this paper.

RESULTS AND DISCUSSION

Synthesis of α-Pyrrylalditols. The first task was the study of the direct coupling reaction between pyrrole and the three-carbon sugar prototype 2,3-*O*-isopropylidene-D-glyceraldehyde (**1**). One of the essential requirements for useful entry to homochiral pyrrylalditols is that we should be able to heteroarylate the sugar at C-1 with a good margin of regio- and stereoselectivity. Disappointingly, treatment of the bromomagnesium salt of pyrrole (PyMgBr) with **1** in CH_2Cl_2 at -80°C resulted in formation of a mixture of several products, from which *erythro* and *threo* α-pyrrylglycerols **2** and **3** were isolated by chromatography in a 1:1 ratio and a low 27% combined yield. However, after some experimentation, we found that the heteroarylation of **1** proceeded very cleanly when a 1:1 blend between PyMgBr and $TiCl(OPr^i)_3$ was used instead of the magnesium salt alone under the same reaction conditions. There was obtained D-*erythro* glycerol **2** in 55% isolated yield along with only minimal amount (ca 8%) of the D-*threo* counterpart **3** (Scheme 1).

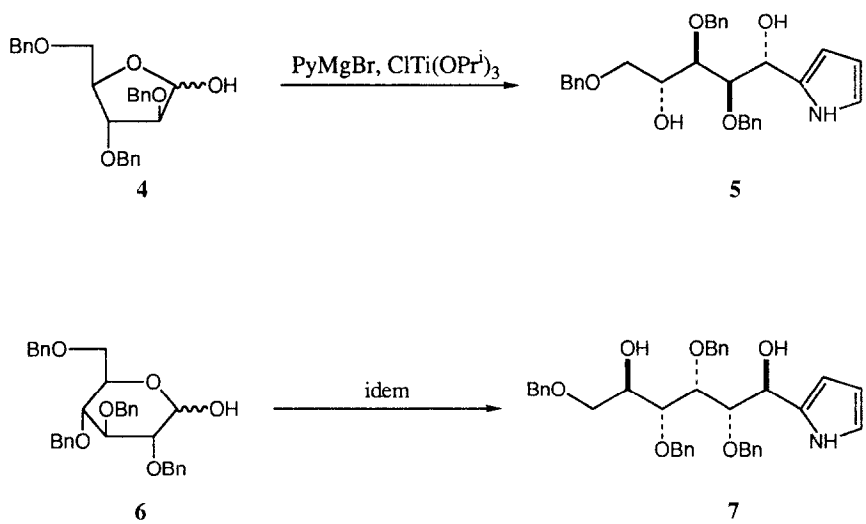
Scheme 1



We next turned our attention to reversal of stereochemistry which would allow selective preparation of D-*threo* glycerol **3**. This was simply achieved by substituting $TiCl(OPr^i)_3$ with coordinating $CeCl_3$ in the reacting metal pyrrole blend.[4] In our hands, coupling between **1** and a 1:1 blend formed by mixing in diethyl ether PyMgBr and $CeCl_3$ afforded, when reacted in CH_2Cl_2 at -80°C, compound **3** in a gratifying 65% yield, accompained by a low quantity of **2** (ca 7%).[5]

These experiments serve to establish that diastereoselective and divergent heteroarylation of a sugar at C-1 with pyrrole is indeed possible by tuning the involved pyrrole metal system. Thus, having a viable heteroarylation protocol, we then extended the reaction to arabinofuranose **4** and glucopyranose **6** bearing free anomeric carbons. Good yields of the corresponding alditolylpyrroles **5** and **7** were obtained by adapting the reaction conditions to the new sugar substrates (Scheme 2).

Scheme 2



4 **5** **6** **7**

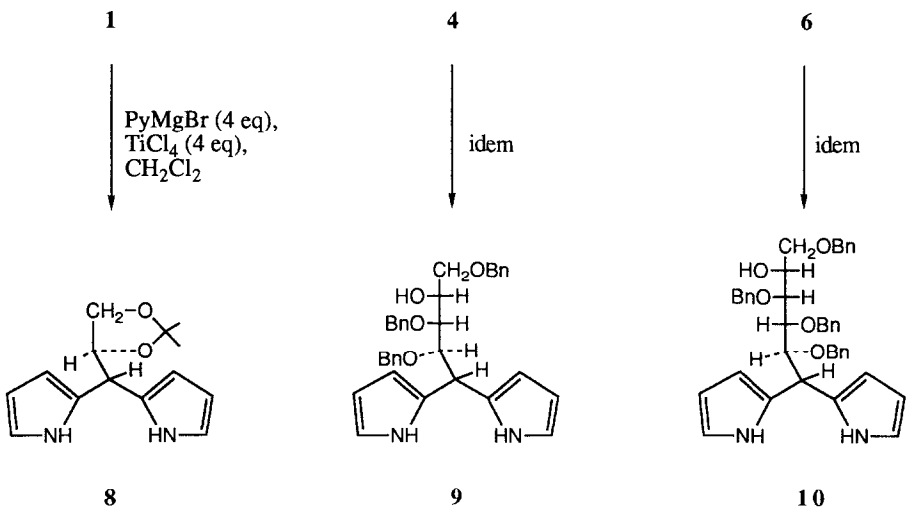
Thus, a PyMgBr-TiCl(OPr^i)$_3$ blend was generated by mixing equimolar amounts of the two components in CH_2Cl_2 at 0°C; the conversion of **4** and **6** was complete within 20h generating, after aqueous quenching, D-*manno* pentitol **5** and D-*glycero*-D-*gulo* hexitol **7** as the sole diastereomers in 64% and 62% isolated yield, respectively.[6] Contrary to that observed for the above reactions involving **1**, attempts to invert the stereochemistry during the carbon-carbon bond formation giving 1',2'-*threo*-configurated derivatives were frustrated since neither PyMgBr alone, nor recourse to strong chelators as $TiCl_4$, $SnCl_4$ or $CeCl_3$ produced detectable amounts of the desired carbinols having the opposite configuration at the newly created stereocenter.

Synthesis of α,α'-Dipyrrylalditols. The formation of methylene- or benzylidene-linked oligonuclear pyrrolic compounds during the pyrrole-aldehyde condensation reactions is a usual matter. If the extension of this chemistry to sugar-related aldehydes or lactols were feasible, a route to enantiomerically pure oligonuclear pyrrolic matrices incorporating chiral alditolyl bridges would be opened. Thus, the condensation between pyrrole and glyceraldehyde **1** was further investigated with this aim. Indeed, after a series of experiments, successful preparation of dipyrromethane **8** was attained by employing an in situ formed 1:1 blend between PyMgBr and $TiCl_4$.[7] Thus, reaction of this blend (4 equiv) in CH_2Cl_2 with **1** at ambient temperature did give rise to **8** as the exclusive product in an acceptable 60% isolated yield (Scheme 3).

Extension of this clean protocol to arabinofuranose **4** and glucopyranose **6** was equally successful,

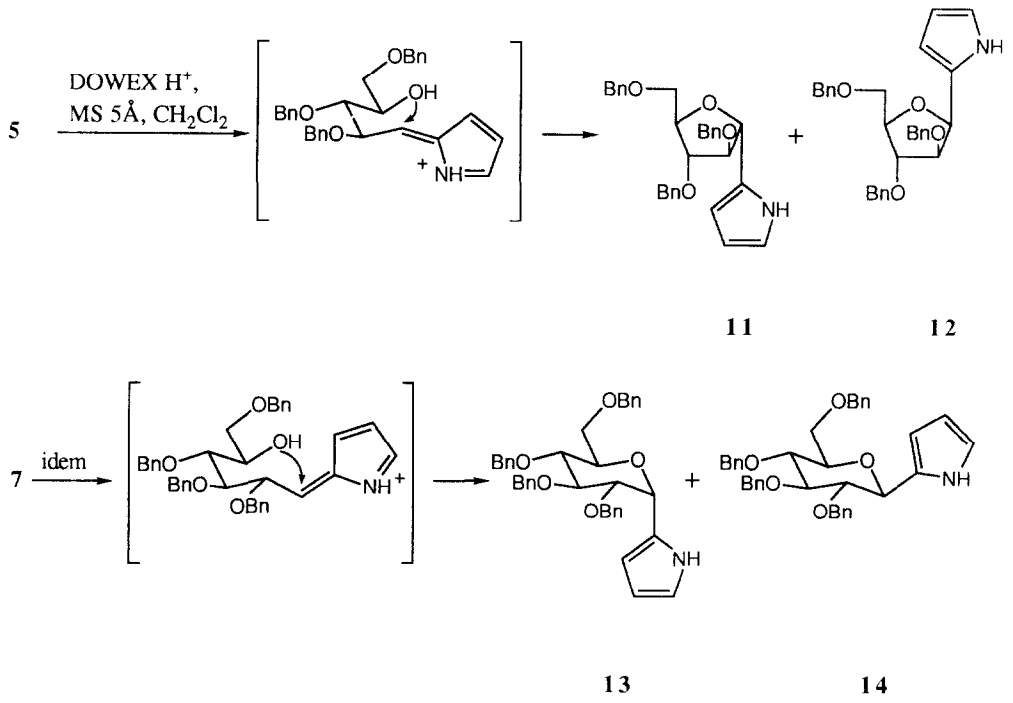
allowing preparation of enantiomerically pure dinuclear compounds **9** and **10** (60% yield each), the structure of which were readily assigned by combined ^1H and ^{13}C NMR spectroscopy and mass spectral measurements. Of note, in the NMR spectra of **8**, **9**, and **10**, separate resonances for the protons and carbons of each pyrrole are observed, indicating the diastereotopic nature of the two rings connected by the chiral alditolyl bridges.

Scheme 3



Synthesis of Pyrrole *C*-Nucleosides. Having substantial amounts of pure alditolylpyrroles **5** and **7**, the preparation of the corresponding cyclic nucleosides was investigated via acid-promoted dehydrative annelation.[8] In both instances, the ring-forming reaction was complete within a week when solutions of the alditols in CH_2Cl_2 were allowed to stir at room temperature in the presence of acidic DOWEX 50x2 resin and powdered 5Å molecular sieves (Scheme 4). Mixtures of anomers were formed, the α-anomer **11** being predominant (51%) over the β-counterpart **12** (29%) for arabinonucleosides, and the β-anomer **14** predominant (50%) over the α-derivative **13** (21%) for gluconucleosides. The individual anomers, easily obtained in a pure state by flash chromatography over SiO_2, were fully characterized by combined spectroscopic methods, including 2D COSY and NOESY techniques. Having both anomers greatly helped in the structural assignment . In particular, in the 2D NOESY maps, for the β-arabinonucleoside **12**, a correlation was observed between H-1' and H-2' and between H-1' and H-4' while, for the α-anomer **11**, H-1' correlates to H-3' and H_2-5', not to H-4'. For the gluconucleoside pair, the configurational assignment was more straightforward. For the β-anomer **14**, in which the pyrrole ring is equatorially disposed, the $J_{1',2'}$=9.4 Hz was very diagnostic whereas for the α-derivative **13**, the $J_{1',2'}$=5.1 Hz indicated the axial location of the heterocyclic moiety.

Scheme 4

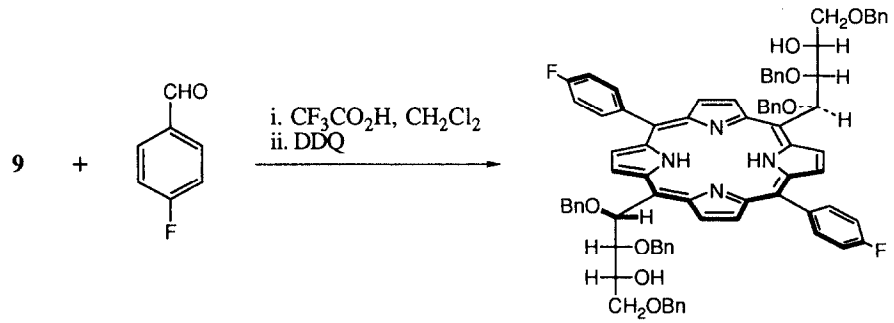


Synthesis of *C*-Glycoconjugated Porphyrins.[9] Homochiral porphyrins and their metallo-derivatives represent promising systems for biomimetic enantioselective catalysis, molecular recognition and binding studies, as well as ligand and ion transport.[10] The idea of synthesizing artificial chiral porphyrin ligands incorporating carbon-linked sugar appendices sprang from the accessibility of appropriate dinuclear building blocks as **9** and **10** by the above route. Thus, the condensation of *p*-fluorobenzaldehyde **15** with dipyrryl derivative **9** was effected in CH_2Cl_2 (10^{-2} M solutions) at room temperature in the dark and in the presence of 10^{-3} M trifluoroacetic acid. Following oxidation of the resultant tetrapyrroles with DDQ, the crude porphyrin was purified by two successive chromatographic operations on SiO_2 eluting with 2% MeOH in CH_2Cl_2 (Scheme 5).

The purified porphyrin **16** (ca 20% yield) was free of other isomers as determined by 1D and 2D COSY NMR analyses. It shows spectra having distinct resonances of chemically equivalent protons for the aryl and alditolyl substituents, while every pyrrolic β-proton has its own resonance, resulting in eight doublets with a coupling constant of ca 4.8 Hz resonating between 8.6 and 10.4 ppm. As expected, a broad signal for the NH protons at approximately -2.5 ppm is present.

The visible absorption maxima (420, 518, 550, 592, 650 nm) are only slightly red-shifted compared with tetraphenylporphyrin (414, 514, 548, 588, 646 nm), suggesting a nearly planar nature of the porphyrin macrocycle.[11]

Scheme 5



15 **16**

CONCLUSIONS

In summary, rational exploitation and tuning of pyrryl metal blends, simply generated in situ by mixing the bromomagnesium salt of pyrrole with titanium^{IV}- or cerium^{III}-based Lewis acid reagents, make it possible to conjugate pyrrole with a sugar via a carbon-carbon bond. This provides a direct regio- and stereoselective approach to either open-chain α-pyrrylalditols or dinuclear α,α'-dipyrryl derivatives which are synthetically useful as precursor of cyclic pyrrole *C*-nucleosides or synthetic porphyrins incorporating carbon-linked sugar appendices, respectively. These novel macrocycles may constitute a promising class of ligands and hosts to be exploited in the asymmetric catalysis, chiral recognition, and transport domains. The significance and synthetic potentiality of the *C*-glycoconjugated pyrrolic structures herein and analogs are now being further investigated.

EXPERIMENTAL SECTION

All the reactions involving pyrrole metal reagents were performed under an argon atmosphere. 2,3-*O*-Isopropylidene-D-glyceraldehyde (**1**) was prepared from commercial 1,2:4,5-di-*O*-isopropylidene-D-mannitol (Aldrich) via periodate cleavage; 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**4**) and 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**6**) were also commercial products (Sigma). ^{1}H NMR spectra were recorded at either 400 MHz or 300 MHz and ^{13}C NMR spectra were recorded at 100.02 or 75.2 MHz. Chemical shifts are reported in parts per million. Fast atom bombardament (FAB) mass spectra were obtained with 3-nitrobenzyl alcohol as the matrix. Optical rotations were measured at room temperature, using the sodium D line. Elemental analyses were performed by the Microanalytical Laboratory of the University of Sassari.

2-(2,3-*O*-Isopropylidene-D-*erythro*-glycerol-1-yl)pyrrole (2). Typical TiCl(OPr^i)$_3$-promoted Procedure. To an ethereal solution of EtMgBr, prepared from Mg (294 mg, 12.28 mmol) and EtBr (1.2 mL) in diethyl ether (50 mL), pyrrole (852 μL, 12.28 mmol) was added under stirring at room temperature. The solvent was then removed under vacuum and CH_2Cl_2 (180 mL) was added to the solid residue. ClTi(OPr^i)$_3$ (12.28 mL of a 1M soln in hexane) was added at -80°C under stirring followed by glyceraldehyde **1** (400 mg, 3.07 mmol), and the resulting slurry was stirred for 6h. Water (300 mL) was added and the organic layer separated and filtered over a celite pad. After drying ($MgSO_4$), the solvent was removed and the residue subjected to flash-chromatography over SiO_2 eluting with a 60:40 hexane/ethyl acetate solvent mixture. This afforded **2**, 0.325 g (55%); an oil, $[\alpha]_D$=+27.4° (*c* 0.84 $CHCl_3$); ^{1}H NMR (300

MHz, $CDCl_3$) δ 8.65 (bs, 1H, NH), 6.76 (m, 1H, H-5), 6.16 (m, 1H, H-3), 6.05 (m, 1H, H-4), 4.91 (d, 1H, *J*=4.2 Hz, H-1'), 4.40 (td, 1H, *J*=6.6, 4.2 Hz, H-2'), 3.98 (dd, 1H, *J*=8.1, 6.6 Hz, H-3_a'), 3.86 (dd, 1H, *J*=8.4, 6.6 Hz, H-3_b'), 2.42 (bs, 1H, OH), 1.45 (s, 3H, Me), 1.39 (s, 3H, Me); ^{13}C NMR (74.2 MHz, $CDCl_3$) δ 129.86, 117.63, 109.63, 108.34, 105.31, 78.45, 67.85, 65.20, 26.42, 25.02. Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 61.10; H, 7.80; N, 7.22.

2-(2,3-*O*-Isopropylidene-D-*threo*-glycerol-1-yl)pyrrole (3). Typical $CeCl_3$-promoted Procedure. To an ethereal solution of EtMgBr, prepared from Mg (294 mg, 12.28 mmol) and EtBr (1.2 mL) in diethyl ether (50 mL), pyrrole (852 μL, 12.28 mmol) was added followed by solid $CeCl_3$ (3.02 g, 12.28 mmol). After being stirred for 1 h at room temperature, the slurry was evaporated under vacuum and then CH_2Cl_2 (180 mL) was added to the residue. Glyceraldehyde **1** (400 mg, 3.07 mmol) was added to this solution at -80°C, and the resulting mixture was stirred for 6 h.Water (300 mL) was added and the mixture extracted with CH_2Cl_2 (3x100mL). After drying ($MgSO_4$), the solvent was removed and the residue was flash-chromatographed over SiO_2 eluting with an hexane/ethyl acetate 60:40 solvent mixture. This afforded compound **3**, 0.38 g, (65%); an oil, $[\alpha]_D$= -20.0° (*c* 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.75 (bs, 1H, NH), 6.75 (m, 1H, H-5), 6.14 (m, 1H, H-3), 6.09 (m, 1H, H-4), 4.61 (dd, 1H, *J*=6.6, 3.3 Hz, H-1'), 4.29 (q, 1H, *J*=6.6 Hz, H-2'), 3.98 (dd, 1H, *J*=8.4, 6.6 Hz, H-3_a'), 3.86 (dd, 1H, *J*=8.4, 6.0 Hz, H-3_b'), 2.82 (d, 1H, J=3.3 Hz, OH), 1.49 (s, 3H, Me), 1.39 (s, 3H, Me); ^{13}C NMR (75.2 MHz, $CDCl_3$) δ 130.11, 118.11, 110.05, 108.32, 106.33, 78.74, 68.93, 66.22, 29.75, 25.30. Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.80; H, 7.78; N, 7.25.

2-(2,3,5-Tri-*O*-benzyl-D-*manno*-pentitol-1-yl)pyrrole (5). Following the typical procedure described for the preparation of compound **2**, by using **4** (1.3 g, 3.0 mmol) as the sugar component and a reaction time of 20h at 0°C, pure **5** was obtained after flash-chomatography over SiO_2 (hexane/acetone 60:40) as an oil, 936 mg (64%), $[\alpha]_D$= +23.9° (*c* 1.3, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (bs, 1H, NH), 7.4-7.2 (m, 15H, CH_2Ph), 6.67 (dd, 1H, *J*= 4.0, 2.4 Hz, H-5), 6.17 (dd, 1H, *J*=5.6, 2.8 Hz, H-3), 6.04 (m, 1H, H-4), 5.05 (d, 1H, *J*=3.8 Hz, H-1'), 4.7-4.3 (m, 6H, CH_2Ph), 4.09 (ddd, 1H, *J*=7.0, 5.2, 3.8 Hz, H-4'), 3.93 (dd, 1H, *J*=4.0, 3.7 Hz, H-2'), 3.73 (dd, 1H, *J*=7.0, 4.4 Hz, H-3'), 3.69 (dd, 1H, *J*=9.8, 3.8 Hz, H-$5'_a$), 3.63 (dd, 1H, *J*=9.7, 5.6 Hz, H-$5'_b$), 3.50 (bs, 1H, OH), 3.0 (bs, 1H, OH); ^{13}C NMR (100.0 MHz, $CDCl_3$) δ 137.93, 131.98, 129-127, 117.26, 108.21, 105.17, 82.70, 78.94, 74.57, 73.85, 71.06, 70.89, 67.75. Anal. Calcd. $C_{30}H_{33}NO_5$: C, 73.90; H, 6.82; N, 2.87. Found: C, 73.75; H, 6.97; N, 2.78.

2-(2,3,4,6-Tetra-*O*-benzyl-D-*glycero*-D-*gulo*-hexitol-1-yl)pyrrole (7). This was obtained according to the above procedure by using **6** (1.6 g, 3.0 mmol) as the sugar component. Pure **7** was isolated by flash-chromatography over SiO_2 (hexane/acetone 80:20); an oil, 1.13 g (62%), $[\alpha]_D$= +2.3 (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.4 (bs, 1H, NH), 7.4-7.2 (m, 20H, CH_2Ph), 6.65 (dd, 1H, *J*= 4.2, 2.7 Hz, H-5), 6.13 (dd, 1H, *J*=6.0, 2.8 Hz, H-3), 5.98 (m, 1H, H-4), 4.90 (dd, 1H, *J*=5.4, 3.6 Hz, H-1'), 4.7-4.3 (m, 8H, CH_2Ph), 4.08 (m, 1H, H-5'), 3.99 (m, 2H, H-2' and H-3'), 3.72 (m, 1H, H-4'), 3.64 (m, 2H, H_2-6'), 3.09 (d, 1H, *J*=5.4 Hz, OH), 3.04 (d, 1H, *J*=5.2 Hz, OH); ^{13}C NMR (100.0 MHz, $CDCl_3$) δ 139.08, 131.75, 129-127, 117.29, 108.30, 105.30, 82.46, 79.38, 77.32, 75.09, 74.73, 73.57, 73.21, 71.28, 70.95, 68.21. Anal. Calcd. for $C_{38}H_{41}NO_6$: C, 75.10; H, 6.80; N, 2.30. Found: C, 74.98; H, 6.90; N, 2.22.

(2S)-2,3-*O*-Isopropylidene-2,3-dihydroxy-1,1-dipyrrylpropane (8). Typical $TiCl_4$-promoted Procedure. To a solution of EtMgBr in diethyl ether (50 mL), prepared from Mg (294 mg, 12.28 mmol) and EtBr (1.2 mL), pyrrole (852 μL) was added under stirring at room temperature. After the ether was removed under vacuum, CH_2Cl_2 (180 mL) was added followed by $TiCl_4$ (12.28 mL of a 1M soln in CH_2Cl_2) at -80°C under stirring. Glyceraldehyde **1** (400 mg, 3.07 mmol) was added to the solution and the resulting mixture was stirred at -80°C for 6 h. Water (300 mL) was added and the mixture extracted with CH_2Cl_2 (3x100 mL). After drying ($MgSO_4$), the solvent was evaporated and the residue was flash-chromatographed over SiO_2 (hexane/ethyl acetate 70:30) to give **8** as an oil; 0.44 g (60%), $[\alpha]_D$=-38.6° (*c* 1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.69 (bs, 1H, NH), 8.17 (bs, 1H, NH), 6.73 (m, 1H, H-5'), 6.70 (m, 1H, H-5"), 6.14 (m, 1H, H-3'), 6.12 (m, 1H, H-3"), 6.08 (m, 1H, H-4'), 5.88 (m, 1H, H-4"), 4.57 (td, 1H, *J*=6.9, 6.3 Hz, H-2), 4.20 (d, 1H, J=7.2 Hz, H-1), 3.97 (dd, 1H, *J*= 8.7, 6.3 Hz, H-3a), 3.68 (dd, 1H, *J*=8.7, 7.2 Hz, H-3b), 1.42 (s, 3H, Me), 1.41 (s, 3H, Me); ^{13}C NMR (75.2 MHz, $CDCl_3$) δ 130.64, 129.32, 117.35, 117.25, 109.74, 108.15, 107.72, 106.96, 106.67, 78.24, 67.94, 41.06, 26.66, 25.59. Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.44; H, 7.54; N, 11.49.

2,3,5-Tri-*O*-benzyl-1-deoxy-1,1-dipyrrylarabinitol (9). This was obtained according to the above procedure for compound **8** by using **4** (1.3 g, 3.0 mmol). Pure **9** was obtained by flash-chromatography (hexane/acetone 80:20); 966 mg (60%), colorless needles, mp 146-148°C, $[\alpha]_D$= -8.7° (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (bs, 1H, NH), 7.70 (bs, 1H, NH), 7.3-7.0 (m, 15H, CH_2Ph), 6.61 (dd, 1H, *J*=4.9, 2.6 Hz, H-5'), 6.44 (dd, 1H, *J*=4.9, 2.6 Hz, H-5"), 6.11 (dd, 1H, *J*=4.8, 2.4 Hz, H-3'), 6.08 (dd, 1H, *J*=5.2, 2.6 Hz, H-3") 5.99 (m, 1H, H-4'), 5.93 (m, 1H, H-4"), 4.5-4.4 (m, 5H, CH_2Ph), 4.36 (d, 1H, *J*=4.5 Hz, H-1), 4.16 (dd, 1H, *J*=4.5, 4.9 Hz, H-2), 4.03 (d, 1H, *J*=10.3 Hz, 1/2 CH_2Ph), 3.92 (m, 1H, H-4), 3.62 (dd, 1H, *J*=9.5, 4.9 Hz, H-3), 3.58 (bs, 1H, OH), 3.52 (m, 2H, H_2-5); ^{13}C NMR (100.0 MHz, $CDCl_3$) δ 138.38, 138.20, 137.79, 131.63, 129.50, 129-127, 117.41, 116.38, 108.39, 108.04, 105.50, 83.63, 80.81, 75.30, 74.51, 73.59, 71.96, 71.11, 39.68. Anal. Calcd. for $C_{34}H_{36}N_2O_4$: C, 76.09; H, 6.76; N, 5.22. Found: C, 75.94; H, 6.85; N, 5.30.

2,3,4,6-Tetra-*O*-benzyl-1-deoxy-1,1-dipyrrylglucitol (10). This was produced according to the above protocol by using **6** (1.6 g, 3.0 mmol). Pure **10** was obtained by flash-chromatography on SiO_2 (hexane/acetone 80:20); 1.18 g (60%), an oil, $[\alpha]_D$= +23.5° (*c* 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.83 (bs, 1H, NH), 7.63 (bs, 1H, NH), 7.4-7.1 (m, 20H, CH_2Ph), 6.70 (m, 1H, H-5'), 6.55 (m, 1H, H-5"), 6.13 (m, 2H, H-3' and H-3"), 5.99 (m, 1H, H-4'), 5.93 (m, 1H, H-4"), 4.7-4.4 (m, 7H, CH_2Ph), 4.33 (dd, 1H, *J*=7.3, 3.3 Hz, H-2), 4.22 (d, 1H, *J*=3.3 Hz, H-1), 4.18 (d, *J*=11.1 Hz, 1/2 CH_2Ph), 4.06 (m, 1H, H-5), 3.7-3.5 (m, 4H, H-3, H-4, H_2-6), 2.91 (bs, 1H, OH); ^{13}C NMR (100.0 MHz, $CDCl_3$) δ 138.45, 138.05, 131.74, 129.81, 128-126, 117.65, 116.21, 108.54, 107.98, 105.33, 83.88, 80.00, 77.43, 75.80, 74.74, 73.49, 72.84, 71.32, 70.72, 39.55. Anal. Calcd. for $C_{42}H_{44}N_2O_5$: C, 76.80; H, 6.75; N, 4.26. Found: C, 76.65; H, 6.90; N, 4.35.

2-(2,3,5-Tri-*O*-benzyl-α-D-arabinofuranosyl)pyrrole (11) and 2-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)pyrrole (12). To a solution of alditol **5** (500 mg, 1.0 mmol) in CH_2Cl_2 (100mL), DOWEX 50x2 resin (H^+ form, 500 mg) and powdered activated 4Å molecular sieves (500 mg) were added at room temperature. The slurry was stirred for 7 days at room temperature and then filtered to remove catalysts.

After removal of the solvent, **11** and **12** were isolated in a pure state by flash-chromatography over SiO_2 eluting with a hexane/acetone 80:20 solvent mixture:

Compound 11, 240 mg (51%), an oil, Rf=0.30, $[\alpha]_D$= -4.15° (*c* 0.2, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (bs, 1H, NH), 7.5-7.1 (m, 15H, CH_2Ph), 6.60 (dd, 1H *J*=4.3, 2.6 Hz, H-5), 6.08 (m, 1H, H-4), 6.04 (dd, 1H, *J*=5.7, 2.8 Hz, H-3), 5.08 (d, 1H, *J*=2.8 Hz, H-1'), 4.7-4.4 (m, 6H, CH_2Ph), 4.31 (m, 1H, H-4'), 4.15 (dd, 1H, *J*=2.8, 2.6 Hz, H-2'), 4.10 (dd, 1H, *J*=2.6, 2.4 Hz, H-3'), 3.59 (dd, 1H, *J*=9.9, 5.3 Hz, H-5'$_a$), 3.54 (dd, 1H, *J*=10.0, 6.5 Hz, H-5'$_b$); ^{13}C NMR (100.0 MHz, $CDCl_3$) δ 137.73, 131.52, 127-129, 116.53, 108.07, 107.54, 87.58, 84.78, 82.26, 79.54, 73.44, 71.98, 70.18. Anal. Calcd. for $C_{30}H_{31}NO_4$: C, 76.73; H, 6.65; N, 2.98. Found: C, 76.64; H, 6.88; N, 3.09.

Compound 12, 135 mg (29%), an oil, Rf=0.37, $[\alpha]_D$= -4.0° (*c* 0.2, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (bs, 1H, NH), 7.4-7.0 (m, 15H, CH_2Ph), 6.58 (dd, 1H, *J*=4.3, 2.6 Hz, H-5), 6.12 (m, 1H, H-4), 6.05 (dd, 1H, *J*=5.8, 2.8 Hz, H-3), 5.03 (d, 1H, *J*=3.9 Hz, H-1'), 4.6-4.1 (m, 6H, CH_2Ph), 4.05 (m, 2H, H-3' and H-4'), 3.94 (dd, 1H, *J*=3.9, 1.7 Hz, H-2'), 3.61 (dd, 1H, *J*=10.0, 4.9 Hz, H-5'$_a$), 3.57 (dd, 1H, *J*=10.0, 4.6 Hz, H-5'$_b$); ^{13}C NMR (100.0 MHz, $CDCl_3$) δ 139.21, 137.63, 131.32, 129-127, 116.70, 108.66, 107.57, 84.72, 83.60, 81.41, 73.46, 71.91, 70.32. Anal. Calcd. for $C_{30}H_{31}NO_4$: C, 76.73; H, 6.65; N, 2.98. Found: C, 76.58; H, 6.76; N, 2.88.

2-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)pyrrole (13) and 2-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)pyrrole (14). These were produced according to the above protocol by starting with alditol **7** (600 mg, 1.0 mmol). The α and β anomers were isolated by flash-chromatography eluting with $CHCl_3$:

Compound 13, 124 mg (21%), an oil, Rf=0.36, $[\alpha]_D$= +30.7° (*c* 0.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) d 8.90 (bs, 1H, NH), 7.4-7.1 (m, 20H, CH_2Ph), 6.65 (m, 1H, H-5), 6.27 (m, 1H, H-3), 6.10 (m, 1H, H-4), 5.25 (d, 1H, *J*=5.16 Hz, H-1'), 4.9-4.4 (m, 8H, CH_2Ph), 3.89 (m, 2H, H_2-6'), 3.4-3.7 (m, 4H, H-2', H-3', H-4', H-5'). Anal. Calcd. for $C_{38}H_{39}NO_5$: C, 77.39; H, 6.67; N, 2.38. Found: C, 77.22; H, 6.80; N, 2.48.

Compound 14, 300 mg (50%), an oil, Rf=0.30, $[\alpha]_D$= +26.9° (*c* 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (bs, 1H, NH), 7.4-7.2 (m, 20H, CH_2Ph), 6.77 (m, 1H, H-5), 6.26 (m, 1H, H-3), 6.18 (m, 1H, H-4), 4.0-5.0 (m, 8H, CH_2Ph), 4.32 (d, 1H, *J*=9.4 Hz, H-1'), 3.76 (m, 4H, H-3', H-4', H_2-6'), 3.53 (m, 1H, H-5'), 3.50 (dd, 1H, *J*=9.8, 9.3 Hz, H-2'); ^{13}C NMR (100.0 MHz, $CDCl_3$) δ 138.89, 129-127, 117.93, 109.34, 108.54, 86.47, 83.17, 79.05, 78.06, 77.03, 75.75, 75.07, 74.64, 73.57, 69.17. Anal. Calcd. for $C_{38}H_{39}NO_5$: C, 77.39; H, 6.67; N, 2.38. Found: C, 77.55; H, 6.87; N, 2.26.

5,15-[Bis-(4-flurophenyl)]-10,20-[bis-(1,2,4-tri-*O*-benzyl-D-*arabino*-tetritol-1-yl)]-porphyrin (16). To a solution of dipyrrylalditol **9** (100 mg, 0.19 mmol) in CH_2Cl_2 (20 mL), *p*-fluorobenzaldehyde (23.56 mg, 0.19 mmol) and CF_3CO_2H (15 μL) were added at room temperature in the dark and the mixture was allowed to react for 3h. DDQ (40 mg, 0.18 mmol) was added and, after 3h, the solvent was removed and the dark brown residue dissolved in a 2% MeOH solution in CH_2Cl_2. After two chromatographic separations, the porphyrin free base **16** was obtained as a dark red powder, 25 mg (20%), mp> 240°C, $[\alpha]_D$= -43.6° (*c* 0.2, $CHCl_3$); FAB Ms, *m/z* 1279; UV-vis ($CHCl_3$) λ_{max} 420 nm (ε = 145 116 cm^{-1} M^{-1}), 518 (ε = 7 674), 550 (ε = 2674), 592 (ε = 2906), 650 (ε = 1907); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (d, 1H, *J* = 4.8 Hz), 10.27 (d, 1H, *J* = 4.9 Hz), 9.39 (d, 1H, *J* = 4.7 Hz), 9.35 (d, 1H, *J* = 4.8 Hz),

8.79 (d, 1H, J = 4.8 Hz), 8.75 (d, 1H, J = 4.8 Hz), 8.74 (d, 1H, J = 4.8 Hz), 8.69 (d, 1H, J = 4.9 Hz), 8.12 (m, 2H), 7.45 (m, 2H), 7.23 (m, 30H), 6.86 (m, 2H), 6.50 (bt, 2H, J = 8.4 Hz), 4.1-4.9 (m, 12H), 3.88 (d, 1H, J = 5.1 Hz), 3.85 (d, 1H, J = 5.1 Hz), 3.6-3.8 (m, 8H), 2.67 (d, 1H, J = 5.8 Hz), 2.60 (d, 1H, J = 5.8 Hz), -2.3 (bs, 2H). Anal. Calcd. for $C_{82}H_{72}N_4O_8F_2$: C, 76.98; H, 5.67; N, 4.38. Found: C, 77.11; H, 5.90; N, 4.49.

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