Pergamon

Tetrahedron Letters 43 (2002) 603–605

TETRAHEDRON LETTERS

# Porphyrins in 1,3-dipolar cycloaddition reactions with sugar nitrones. Synthesis of glycoconjugated isoxazolidine-fused chlorins and bacteriochlorins

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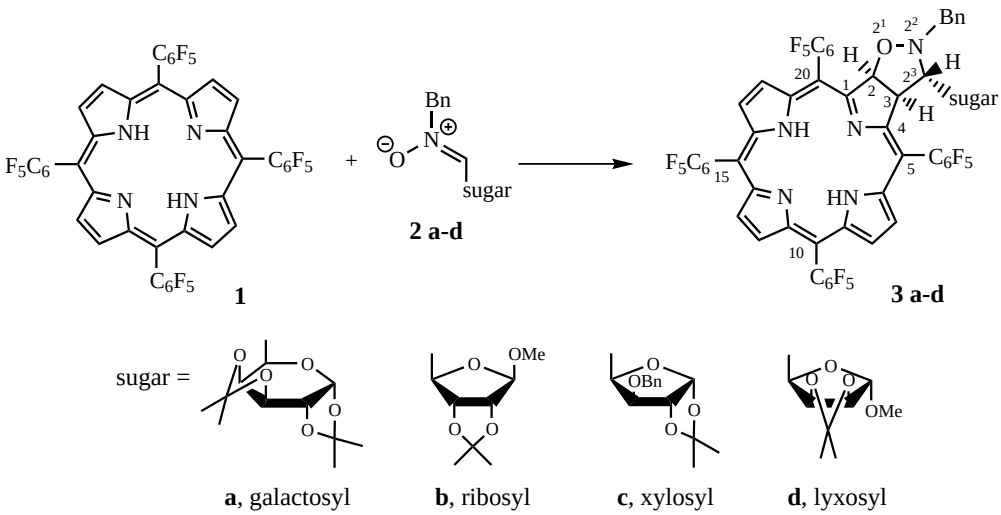
Received 2 November 2001; revised 22 November 2001; accepted 23 November 2001

**Abstract**—Glycoconjugated isoxazolidine-fused chlorins and bacteriochlorins were prepared in moderate to good yields by 1,3-dipolar cycloaddition reactions of *meso*-tetrakis(pentafluorophenyl)porphyrin with glycosyl nitrones. 

In recent years, a number of carbohydrate derivatives of porphyrins have been synthesized and tested as photosensitizers in the photodynamic therapy (PDT) of cancer.[1] Such conjugates have demonstrated a good solubility and selectivity to the cancer cells. On the other hand, for a deep penetration of the light into tissue is required a photosensitizer with a strong absorption in the visible region near or above 650 nm, like chlorins and bacteriochlorins. Bacteriochlorins with significant absorptions at $\lambda$>700 nm do play a key role in such processes. Recently, some of us have developed methodologies for the synthesis of such types of compounds using *o*-quinodimethanes,[2] azomethine ylides,[3] and nitrones.[4] We are now extending the 1,3-dipolar cycloaddition approach to synthesize novel glycoderivatives of the chlorin (**3**) and bacteriochlorin (**4** and **5**) types by reaction of *meso*-tetrakis(pentafluoro phenyl)porphyrin **1** with several readily available sugar nitrones **2**.[5]




**Scheme 1.**

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0040-4039/02/$ - see front matter 
PII: S0040-4039(01)02243-2

The first model reaction was performed by heating at 60°C a mixture of porphyrin **1** and an excess of galactosyl nitrone **2a**, in a small volume of toluene.[6] After five days, the reaction afforded a mixture of three compounds which were separated by column chromatography and preparative TLC. The major product (66% yield), the one with higher $R_f$, shows a UV–vis spectrum typical of a chlorin ($\lambda_{max}=646$ nm) and its FAB mass spectrum ($M^{+\bullet}=1337$) indicates that it is a 1:1 adduct. These data and its NMR spectrum are consistent with the structure of chlorin **3a**.[7] The coupling constants $J_{H2-H3}=8.2$ Hz and $J_{H3-H2^3}=0$ Hz support the configuration shown in Scheme 1. The configuration of this compound indicates an *endo* addition.[8]

The two other products of the reaction showed identical mass spectra [$(M+H)^+=1701$] indicating the addition of two nitrone residues to the porphyrin macrocycle. The UV–vis spectra ($\lambda_{max}=709$ nm) of these compounds showed that they are both bacteriochlorins. Since the nitrone bis-addition to the porphyrin macrocycle can lead to structures **4** or **5** (Fig. 1), four diastereomeric bacteriochlorins are possible (assuming that both additions are *endo*). The $^1$H NMR spectrum of the major one (21% yield)[9] showed one singlet at $\delta$ −2.37 (NH protons) and one AB spin system corresponding to the resonance of the four β-pyrrolic protons. This spectrum is only compatible with structures **4**. The $^1$H NMR spectrum[10] of the minor bacteriochlorin (9% yield) showed two singlets at $\delta$ −2.37 and −2.23 corresponding to the NH protons and one multiplet at $\delta$ 8.45–8.47 for the four β-pyrrolic protons. The difference observed in the resonances of the two NH protons indicates that the chemical environment of these protons is quite different; this is consistent with structures **5**. Several attempts to obtain crystals of the two bacteriochlorin products for an X-ray diffraction analysis failed so far and the final differentiation between structures **4.1** and **4.2** and also between **5.1** and **5.2** still remains to be made.

It is noteworthy that the product distribution of the reaction of **1** with **2a** is quite affected by the reaction time: a shorter reaction time (four days) leads to an increased yield of chlorin **3a** (74%) at expenses of the mixture of bacteriochlorins (18%). Moreover it was possible to obtain the bacteriochlorins by treatment of the chlorin **3a** with an additional amount of sugar nitrone **2a**.

The cycloaddition of other sugar nitrones to porphyrin **1** also led to the corresponding chlorins **3** and, in some cases, to bacteriochlorins. The reaction with ribosyl nitrone **2b** (60°C, 5 days) is quite stereoselective giving rise to the chlorin **3b** (30% isolated yield). With xylosyl nitrone **2c** (100°C, 10 h) the reaction led to the chlorin **3c** (37% isolated yield) and to a very small amount of a bacteriochlorin as judged by the mass [$(M+H)^+=1741$] and UV–vis spectra ($\lambda_{max}=709$ nm). Unfortunately, the formation of this compound could not be improved under different reaction conditions (temperature, time) and addition of small amounts of nitrone to the crude reaction mixture. However we were pleased to observe that the reaction with lyxosyl nitrone **2d** (80°C, two days) afforded, as the major product, a single bacteriochlorin in very good yield (61%) and the chlorin **3d** in 29% yield. The formation of a single bacteriochlorin is noteworthy since as stated before the bis-addition can lead to four possible stereomers (Fig. 1). The $^1$H NMR

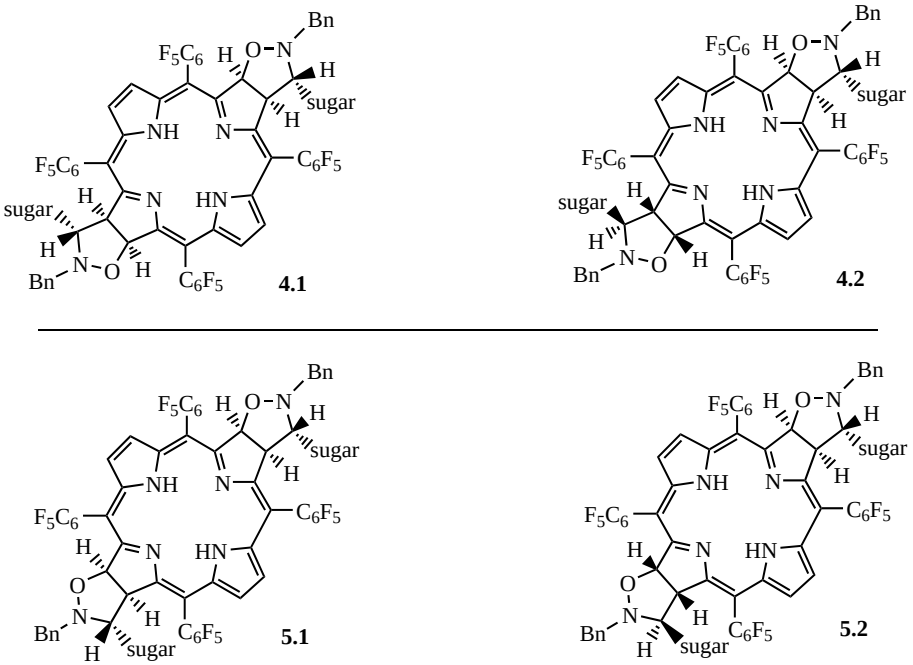


**Figure 1.**

spectrum of this compound showed one broad singlet at $\delta$ −2.31 corresponding to the NH protons and an AB spin system at $\delta$ 8.44 and 8.48 (two dd, $J=4.9$ and 1.3 Hz) corresponding to the resonances of four β-pyrrolic protons. This $^1$H NMR spectrum is compatible with structures **4**.

Cleavage of the isopropylidene acetals in chlorin and bacteriochlorin adducts was carried out in aqueous solution of trifluoroacetic acid to afford the respective free products in quantitative yields.

In conclusion, a new class of porphyrin glycoconjugates was obtained. Of special importance are the bacteriochlorin derivatives which, because of their strong absorption in the visible region above 700 nm, become very promising for their potential application as photosensitizers in the PDT of cancer. The results of biological tests, which are underway, will be published in due course.

## Acknowledgements

Thanks are due to the University of Aveiro and to 'Fundação para a Ciência e a Tecnologia-FCT', Lisbon, for funding the Organic Chemistry Research Unit and Project POCTI/1999/QUI/32851. One of us (A. M. G. Silva) also thanks FCT for a Ph.D. grant. The financial support of the University of Ferrara is also gratefully acknowledged.

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6. General procedure for the 1,3-dipolar cycloadditions with sugar nitrones: the *meso*-tetrakis(pentafluoro phenyl)porphyrin **1** (0.01 mmol), the sugar nitrone **2** (0.04 mmol; except for ribosyl nitrone **2b** where 0.06 mmol were used instead) and toluene (a few drops), under a nitrogen atmosphere, were heated in a closed vessel at 60–100°C for 2–5 days. After cooling to rt, the resulting residue was purified by flash chromatography using a mixture of cyclohexane/dichloromethane (2:3) as eluent. When necessary, the fraction of the bacteriochlorins was further purified by preparative TLC using toluene/ethyl acetate (99:1) as eluent.
7. Spectroscopic data for chlorin **3a**: $^1$H NMR (300 MHz, $CDCl_3$, $J$ in Hz) $\delta$: −2.10 (s, 2 H, NH), 0.96, 1.19, 1.38 and 1.58 (4s, 12 H, 4×$CH_3$), 2.34 (d, 1 H, $J$ 12.0, C$H_2$C$_6$H$_5$), 3.29 (d, 1 H, $J$ 12.0, C$H_2$C$_6$H$_5$), 3.71 (d, 1 H, $J$ 10.6, H-5-sugar), 4.12 (d, 1 H, $J$ 10.6, H-2$^3$), 4.24 (dd, 1 H, $J$ 4.8 and $J$ 1.7, H-2-sugar), 4.30 (dd, 1 H, $J$ 8.2 and $J$ 0.9, H-4-sugar), 4.41 (dd, 1 H, $J$ 8.2 and $J$ 1.7, H-3-sugar), 5.36 (d, 1 H, $J$ 4.8, H-1-sugar), 5.88 (d, 1 H, $J$ 8.2, H-3), 6.27 (d, 2 H, $J$ 7.4, H$_{ortho}$-Ph), 6.86 (d, 1 H, $J$ 8.2, H-2), 6.80–6.91 (m, 3 H, H$_{meta+para}$-Ph), 8.57 (d, 2 H, $J$ 4.6, H-β), 8.58 (s, 2 H, H-12, 13), 8.82–8.85 (m, 2 H, H-β); MS (LSIMS): 1337 ($M^{+\bullet}$), 974 (starting porphyrin)$^{+\bullet}$; UV–vis ($CH_2Cl_2$) $\lambda_{max/nm}$: 646 (24%), 593 (4%), 529 (4%), 502 (10%), 404 (100%).
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9. Major bacteriochlorin (**4.1** or **4.2**): $^1$H NMR (300 MHz, $CDCl_3$, $J$ in Hz) $\delta$: −2.33 (br s, 2 H, NH), 0.94, 1.19, 1.36 and 1.55 (4s, 24 H, 8×$CH_3$), 2.62 (d, 2 H, $J$ 12.1, C$H_2$C$_6$H$_5$), 3.45 (d, 2 H, $J$ 12.1, C$H_2$C$_6$H$_5$), 3.66 (d, 2 H, $J$ 10.6, H-5-sugar), 4.14 (d, 2 H, $J$ 10.6, H-2$^3$), 4.22 (dd, 2 H, $J$ 4.8 and $J$ 1.8, H-2-sugar), 4.28 (dd, 2 H, $J$ 8.1 and $J$ 1.1, H-4-sugar), 4.40 (dd, 2 H, $J$ 8.1 and $J$ 1.8, H-3-sugar), 5.34 (d, 2 H, $J$ 4.8, H-1-sugar), 5.74 (d, 2 H, $J$ 8.5, H-3, 13), 6.42 (d, 4 H, $J$ 7.0, H$_{ortho}$-Ph), 6.72 (d, 2 H, $J$ 8.5, H-2, 12), 6.82–6.95 (m, 6 H, H$_{meta+para}$-Ph), 8.43 (dd, 2 H, $J$ 5.3 and 1.7, H-$\beta$), 8.46 (dd, 2 H, $J$ 5.3 and 1.7, H-β); MS (LSIMS): 1701 $(M+H)^+$, 1700 $M^{+\bullet}$, 1338 (chlorin+H)$^+$, 974 (starting porphyrin)$^{+\bullet}$; UV–vis ($CH_2Cl_2$) $\lambda_{max/nm}$: 709 (61%), 648 (7%), 507 (34%), 478 (6%), 445 (6%), 378 (100%).
10. Minor bacteriochlorin (**5.1** or **5.2**): $^1$H NMR (300 MHz, $CDCl_3$, $J$ in Hz) $\delta$: −2.37 (br s, 1 H, NH), −2.23 (br s, 1 H, NH), 0.95, 1.18, 1.36 and 1.55 (4s, 24 H, 8×$CH_3$), 2.41 (d, 2 H, $J$ 12.1, C$H_2$C$_6$H$_5$), 3.35 (d, 2 H, $J$ 12.1, C$H_2$C$_6$H$_5$), 3.66 (d, 2 H, $J$ 10.5, H-5-sugar), 4.07 (d, 2 H, $J$ 10.5, H-2$^3$), 4.21 (dd, 2 H, $J$ 4.8 and $J$ 1.6, H-2-sugar), 4.29 (d, 2 H, $J$ 8.1, H-4-sugar), 4.39 (dd, 2 H, $J$ 8.1 and $J$ 1.6, H-3-sugar), 5.34 (d, 2 H, $J$ 4.8, H-1-sugar), 5.75 (d, 2 H, $J$ 8.6, H-3, 12), 6.31 (d, 4 H, $J$ 7.3, H$_{ortho}$-Ph, 6.74 (d, 2 H, $J$ 8.6, H-2, 13), 6.81–6.95 (m, 6 H, H$_{meta+para}$-Ph), 8.45–8.47 (m, 4 H, H-β); MS(LSIMS): 1701 $(M+H)^+$, 1700 $M^{+\bullet}$, 1338 (chlorin+H)$^+$, 974 (starting porphyrin)$^{+\bullet}$; UV–vis ($CH_2Cl_2$) $\lambda_{max/nm}$: 709 (62%), 648 (7%), 507 (34%), 478 (6%), 446 (5%), 379 (100%).