Tetrahedron Letters, Vol. 33, No. 12, pp. 1629-1632, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press Ltd

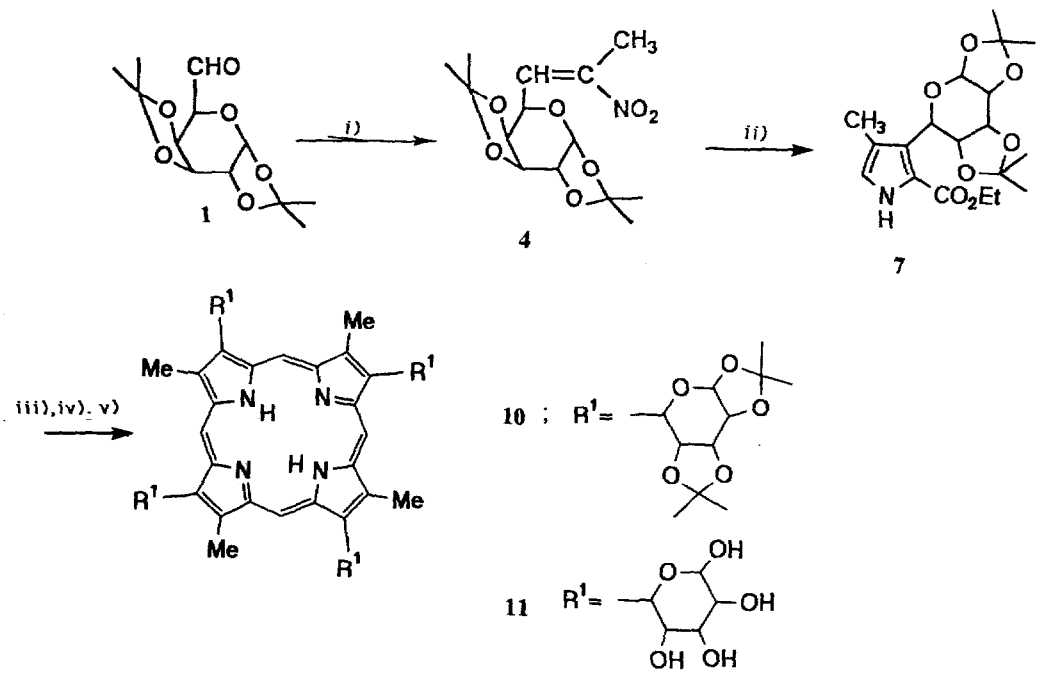
Water-Soluble Porphyrins with Four Sugar Molecules

Noboru Ono,* Masahiro Bougauchi,[+] and Kazuhiro Maruyama[+]
Department of Chemistry, Faculty of Science, Ehime University, Matsuyama 790, Japan
[+]Department of Chemistry, Faculty of Science, Kyoto University, Kyoto 606, Japan

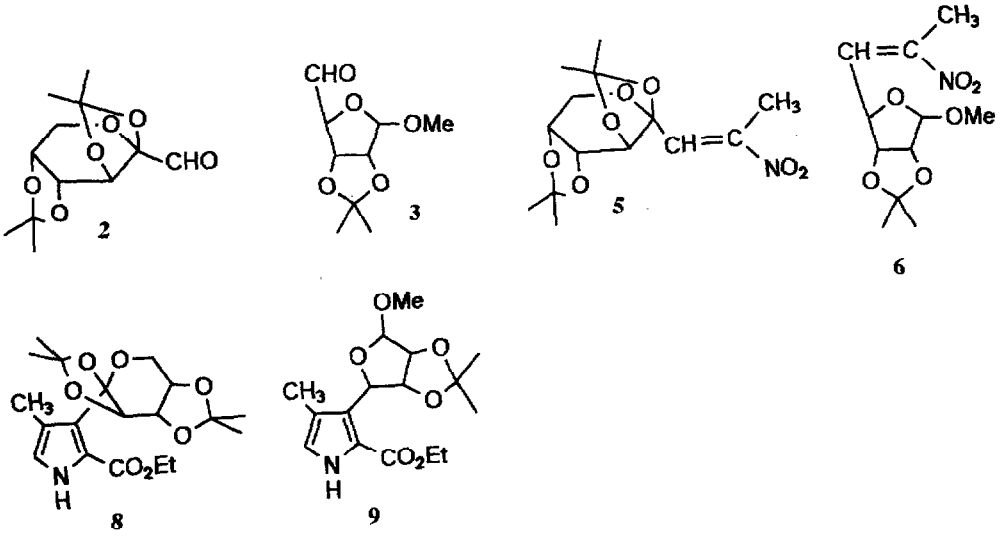
Summary: Porphyrins substituted with four sugar moieties are prepared, which are freely soluble in water and show the efficient photosensitizing activity.

Water soluble porphyrins were recently found to be of great interest because of their strong affinity for cancer cells.[1] In fact Photofrin II, a purified version of hematoporphyrin derivative which localizes in tumors, is currently in phase III clinical trials.[2] In addition to their applications in cancer chemotherapy, porphyrin speciees also appear to exhibit antiviral activity.[3] Furthermore, porphyrins have been used for cancer diagnosis by NMR imaging, for various metals are readily incorporated into porphyrins and porphyrins are selectively taken up by tumors.[4] Therefore a number of water-soluble porphyrins have been studied so far, and most of them have ionic structures.[5] It has been shown that cationic or anionic porphyrins have strong affinities to DNA but the interaction to cells may be different from that of neutral ones.[6] Porphyrins with sugar moieties should be of great importance, because they have not only good solubility in water but also different membrane interaction. A few porphyrins having sugar molecules have been prepared, where porphyrins and sugar molecules are connected by an appropriate linkage such as ester or ether linkages.[7] In this paper we wish to report the first examples of another class of water-soluble porphyrins, where four sugar molecules are directly attached to a porphyrin ring.

The aldehydes **1**, **2** and **3** derived from galactose, fructose and ribose were converted into the corresponding nitroalkenes **4**, **5** and **6** by the condensation with nitroethane in 63-76% yields. The condensation reaction was carried out by heating a mixture of the aldehyde, nitroethane, methyl orthoformate, methylamine hydrochloride, and potassium acetate in methanol at 60 °C for 4 h. Synthesis of pyrroles from nitroalkenes were carried out by the modified procedure of the literature.[8] Treatment of the nitroalkenes with ethyl isocyanoacetate in the presence of DBU (5 equivalents) for 8 h at room temperature gave pyrrole **7**, **8** and **9** in 63%, 67% and 49% yield, respectively. Pyrrole **7**: mp 185-187 °C, ^{1}H NMR ($CDCl_3$) δ = 8.75 (s, 1H, NH), 6.65 (d, 1H, 5-H), 5.76 (d, 1H, 5'-H), 5.66 (d, 1H, 1'-H), 4.67 (dd, 1H, 4'-H), 4.44 (dd, 1H, 2'-H), 4.30 (q, 2H, OCH_2), 2.24 (s, 3H, 4-Me), 1.59, 1.52, 1.36, 1.31 (s, 3H x 4), 1.33 (t, 3H, OCH_2CH_3). Pyrrole **8**: yellow oil, ^{1}H NMR ($CDCl_3$) δ = 9.09 (s, 1H), 6.52 (d, 1H), 5.78 (d, 1H), 4.55 (dd, 1H), 4.30 (q, 2H), 4.00 (dd, 2H), 2.27 (s, 4H), 1.50, 1.40, 1.23, 1.06 (s, 3H x 4), 1.28 (t, 3H). Pyrrole **9**: mp 33-35 °C, ^{1}H NMR ($CDCl_3$) δ = 8.83 (s, 1H), 6.67 (d, 1 H), 5.79 (d, 1 H), 5.05-4.60 (m, 3H), 4.30 (q, 2H), 3.30 (s, 3H, OMe), 2.27 (s, 3H, 4-Me), 1.50, 1.28 (s, 3H x 2), 1.33 (t, 3H). The reduction of **7** by $LiAlH_4$ followed by the acid-catalyzed tetramerization and oxidation with chloranil gave the porphyrin **10** in 18% yield.[9] ^{1}H-NMR spectra of **10** show that type I porphyrin is selectively formed, for protons of meso-positions and β-Me appears at 10.33 and 3.73 ppm as sharp singlets, respectively. In general, tetramerization of unsymmetrical pyrroles gives a mixture of four

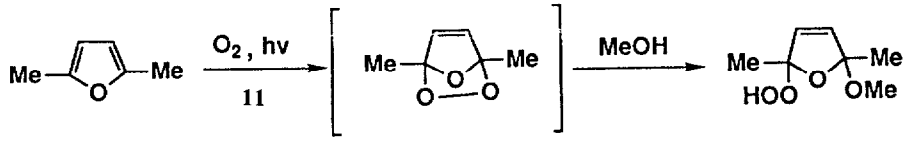


i) AcOK, $CH(OCH_3)_3$, NH_3MeCl, MeOH, reflux4 h.
ii) $CNCH_2CO_2Et$, DBU, THF, room temp 8h.
iii) $LiAlH_4$, 0°C⟶ room temp 2 h.
iv) p-TsOH , room temp 10 h.
v) p-chloranil , room temp 3 h.



possible isomers of porphyrins. The isomerization should be suppressed, because sugar molecules are sterically hindered. However, other pyrroles **8** and **9** could not be converted into porphyrins in good yields by the same procedures. Absorption spectra of the products indicated the formation of porphyrins, but pure porphyrins could not be isolated from the reaction of **8** and **9**. Although the reason for difficulties of conversion of **8** and **9** into porphyrins is not clear at the present stage, it may be due to steric effects in the case of **8**. Thus the choice of the sugar moieties is important to get porphyrins in good yields by the present method. The protection groups in **10** was removed by treatment with cation exchange resin, Amberlite IR-120, in refluxing water saturated with chloroform for 5 h to give porphyrin **11**, which was freely soluble in water. Uv-vis: λ_{max} (H_2O) 403, 502, 438, 563, 614 nm. Porphyrin **11** can be converted into the metalloporphyrins on treatment with metal salts in water. For example, Zn-**11** and Cu-**11** are formed by the reaction of **11** with $Zn(OAc)_2$ and $CuSO_4$ in water; λ_{max} 401, 525, 560 nm for Zn-**11** and 401, 531, 568 nm for Cu-**11** in H_2O.

In order to determine the photosensitizing activity of **11**, the trapping reaction of singlet oxygen with 2,5-dimethylfuran was carried out.[10] The solution of 2,5-dimethylfuran (5 mmol) and **11** (0.005 mmol) in 60 ml of methanol is irradiated with a 150-W tungsten lamp for 60 min at 0 ° C, while air is bubbled through the solution to give **12** in 20% yield. Control experiments with Rose Bengal and hematoporphyrin as an sensitizer and without give **12** in 40% and 25% yield, respectively. Thus, **11** is almost as efficient as Rose Bengal and hematoporphyrin, which are the well known photosensitizers to produce singlet oxygen. As porphyrin **11** may have different affinity to cancer cells from known porphyrins such as hematoporphyrin, it may find biological utility. Further work, directed on studies of chemotherapy of **11**, is now in progress.



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Acknowledgement: This work is supported by Grant-in-Aid for Science Research from the Ministry of Education, Science and Culture of the Japanese Government.

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(Received in Japan 29 November 1991)