Tetrahedron Letters, Vol. 33, No. 52, pp. 8081-8084, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

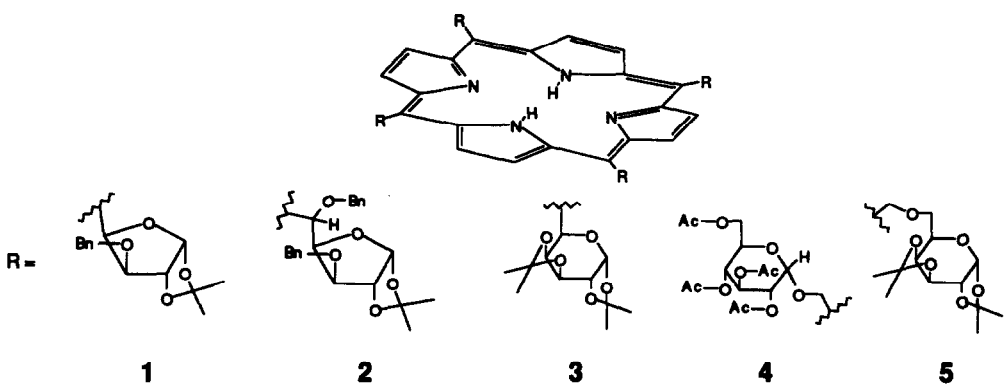
Synthesis of New *Meso*-Tetrakis (Glycosylated) Porphyrins

Ph.Maillard, C.Huel and M.Momenteau*.

Institut Curie, Section de Biologie, Laboratoire Associé au CNRS et Unité INSERM, Bât 112,
Centre Universitaire, 91405 ORSAY, FRANCE

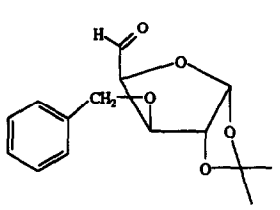
***Abstract**: The synthesis of a new family of meso-tetrakis (glycosylated) porphyrins is reported. Unfortunately, the porphyrins 4 and 5 bearing glycosyloxymethylene substituents are unstable.*

The chemistry of porphyrins bearing glycosylated groups has made rapid progress during last years owing to the development of catalysts for dioxygen activation[1] and of new photosensitizers applied to cancer photochemotherapy[2]. For the catalysis approach superstructured tetraphenylporphyrins have been synthetized in which *meso*-phenyl groups are substituted by steric hindered protected sugars[1]. These structures prohibit the close contact between two macrocycles and give stereoselectivity in alkene oxidation. On the other hand non ionic glycosylated derivatives of porphyrins or other tetrapyrrolic macrocycles could be an intense research way in cancer photochemotherapy because their potential affinity for cancer cells[3]. In contrast, in spite of the great interest in the chemistry of *meso*-substituted porphyrins, no compound had been prepared with glycosyl substituents linked on to *meso*-carbons of macrocycle. We report here the preparation and characterization of some new porphyrins where four protected sugar substituents are directly linked on to these *meso*-positions.

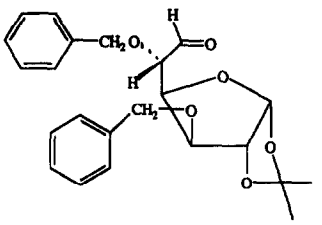


The classical synthesis of *meso*-tetrasubstituted porphyrins consists in the condensation of pyrrole and aldehyde under acid catalysis[4]. The aldehydes **6-10** are the key molecules for the synthesis of porphyrins **1-5**. The aldehyde **6** derived from 1,2-5,6-di-O-isopropylidene-α-D-glucose by methods described in the literature[5,6]. The aldehyde **7** was obtained by one-carbon stereospecific homologation of compound **6** with 2-trimethylsilylthiazole as diastereoselective formyl anion equivalent by the method of Dondoni *et al*[7]. The aldehyde **8** was obtained by oxydation of 1,2-3,4-di-O-isopropylidene-D-galactopyranose with pyridinium

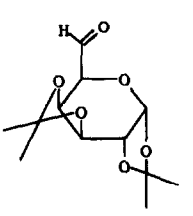
chloride in DMSO in the presence of DCCI[8]. The aldehyde **9** was synthetized from α,D-tetraacetylglucopyranosyl bromide by two steps in 26% overall yield. The first reaction correspond to the condensation of the protected bromo sugar with allylic alcohol under Koenig-Knorr conditions[9]. Subsequent ozonolysis of the β-allyl compound **11**[10] in methylene chloride at -80°C quantitatively gave the aldehyde **9**[11]. The aldehyde **10**[12] was obtained in the same manner as **9** by using the 6-allyl derivative **12**[13] of 1,2-3,4-di-O-isopropylidene-D-galactopyranose as starting material in 13% yield.



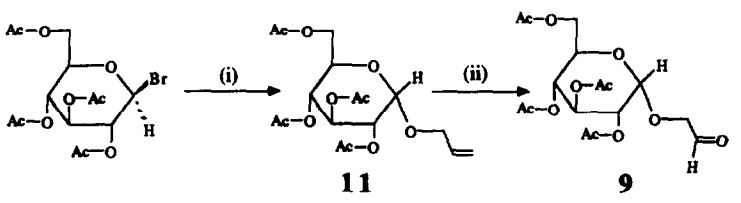
6



7

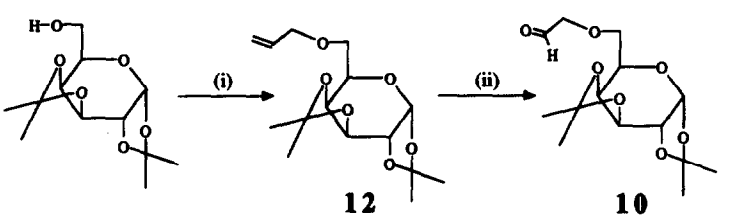


8



11 **9**

(i) Allylic alcohol/Ag_2CO_3/dry ether, (ii) O_3/CH_2Cl_2/-80°C



12 **10**

(i) allyl bromide/C_6H_6/NaH/4 hours, (ii) O_3/CH_2Cl_2/-80°C

Aldehyde **6-10** were used immediately after preparative purification work-up. The condensation reaction was carried out following the Lindsey's method[4] by treatment of a mixture of the appropriate aldehyde and pyrrole in methylene chloride with BF_3/etherate as catalyst under argon at room temperature. Corresponding glycosylated porphyrins **1-5** were obtained by slow oxidation of the intermediate porphyrinogens by treatment of the reactionnal mixtures with chloranil. Porphyrins **1-3** bearing a xylofuranose, a glucofuranose and a galactopyranose respectively as *meso*-substituents were recovered by column chromatography on silica gel using toluene-acetone or methylene chloride-acetone (10/1, v/v) as eluents in 4% yield. On the contrary, the porphyrins **4** and **5** which were detectable by UV-visible spectroscopy were not stable. The reasons that explain the instability of these porphyrins is not clear at this present stage.

Thus, only the porphyrins **1-3** were fully characterized by UV-visible and ^1H NMR spectroscopies[14]. UV-visible spectra of **1**, **2** and **3** are identical to those of *meso*-tetraalkyl porphyrins indicating no electronic

effect of the *meso*-sugar substituents. In ^1H nmr spectroscopy, the chemical shifts of the protons of isopropylidene protective groups and sugars are shifted at low field in comparison with those of corresponding aldehydes and the chemical shifts of the protons of the benzylidene groups are shifted high field. This indicates that the cycle of sugar remains in the porphyrin plan and benzylidene groups are under influence of the ring current of the macrocycle.

In conclusion, we have demonstrated that it is possible to achieve the synthesis of *meso*-tetrakis (glycosylated) porphyrins. The stability of these compounds are largely dependent on the nature of the chain linking the sugars to the porphyrin *meso*-carbons.

References and Notes

1 Maillard Ph., Guerquin-Kern J.L., and Momenteau M. *Tetrahedron Lett.* **1991**, *32*, 4901-4904.

2 Maillard Ph., Guerquin-Kern J.L., Momenteau M., and Gaspard S. *J. Amer. Chem. Soc.* **1989**, *111*, 9125-9127.
Fülling G., Schröder D., and Franck B. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1519-1521.
Kuroda Y., Hirosige T., Sera T., Shiriwa Y., Tanaka H., and Ogoshi H. *J. Amer. Chem. Soc.* **1989**, *111*, 1912-1913.
Kuroda Y., Hirosige T., Sera T., and Ogoshi H. *Carbohyd. Res.* **1989**, *192*, 347-350.
Bonnet R., Nizhnik A.N., and Berenbaum M.C. *J. Chem. Soc. Chem. Commun.* **1989**, 1822-1823.
Bourhim A., Czernercki S., Krausz P., Viari A., and Vigny P. *J. Carbohyd. Chem.* **1990**, *9*, 761-765.
Kus P., Knerr G., and Czuchajowski L. *Tetrahedron Lett.* **1990**, *31*, 5133-5134.
Ono N., Bougauchi M., and Maruyama K. *Tetrahedron Lett.* **1992**, *33*, 1629-1632.
Kohata K., Yamaguchi Y., Higashio H., Odashima T., and Ishii H. *Chem. Lett.* **1992**, 477-480.
Czuchajowski L., Habdas J., Niedbala H., and Wandrekar V. *J. Heterocyclic Chem.* **1992**, *29*, 479-486.

3 Field R.J. *J. Biomol. Struct. Dyn.* **1989**, *6*, 1259-1274 and references therein.
Prinsep M.R., Caplan F.R., Moore R.E., Patterson G.M.L., and Smith C.D. *J. Amer. Chem. Soc.* **1992**, *114*, 385-387.

4 Lindsey J.S., Schreiman I.C., Hsu H.C., Kearney P.C., and Marguerettaz A.M. *J. Org. Chem.* **1987**, *52*, 827-836.
Lindsey J.S., and Wagner R.W. *J. Org. Chem.* **1987**, *54*, 828-836.

5 Brimacombe J.S., and Ching O.A. *Carbohyd. Res.* **1968**, *8*, 82-88.

6 Anderson R.C., and Fraser-Reid B. *J. Org. Chem.* **1985**, *50*, 4785-4790.

7 Medici A., Fantin G., Fogagnolo M., and Dondoni A. *Tetrahedron Lett.* **1983**, *24*, 2901-2904.
Dondoni A., Fogagnolo M., Medici A., and Pedrini P. *Tetrahedron Lett.* **1985**, *26*, 5477-480.
Dondoni A., Fantin G., Fogagnolo M., and Medici A. *Angew. Chem. Int. Ed. Engl.* **1986**, *256*, 835-837.
Dondoni A., Fantin G., Fogagnolo M., and Medici A. *Tetrahedron* **1987**, *43*, 3533-3539.

8 Howarth G.B., Szarek D.G., and Jones J.K.N. *Can. J. Chem.* **1969**, *47*, 75-79.

9 Gigg R., and Warren C.D. *J. Chem. Soc.* **1965**, 2205-2210.

10 ^1H nmr of compound **11** ($CDCl_3$) δ ppm: 5.83 m (1H C<u>H</u>=CH_2), 5.23 d (2H C<u>H</u>$_2$=CH), 5.01 m (3H H_3, H_4, H_2 sugar), 4.54 d (1H H_1 sugar), 4.10 m (4H OCH_2 and H_6 sugar), 3.67 m (1H H_5), 2.07 s (3H CH_3), 2.03 s (3H CH_3), 2.00 s (3H CH_3), 1.99 s (3H CH_3).

11 ^1H nmr of compound **9** ($CDCl_3$) δ ppm: 9.62 t (1H CHO), 5.11 m (3H sugar), 4.56 d (1H H_1 sugar), 4.15 m (3H OCH_2 and H sugar), 3.70 m (2H H_6 sugar), 2.06 s (6H CH_3), 2.00 m (6H CH_3).

12 ^1H nmr of compound **10** ($CDCl_3$) δ ppm: 9.72 t (1H CHO), 5.53 t (1H sugar), 4.59 dd (1H sugar), 4.29 m (2H sugar), 4.23 d (1H sugar), 3.76 m (4H sugar), 1.51 s (3H CH_3), 1.42 s (3H CH_3), 1.31 s (6H CH_3).

13 ^1H nmr of compound **12** ($CDCl_3$) δ ppm: 5.90 m (1H C<u>H</u>=CH_2), 5.54 d (1H sugar), 5.25 d (1H sugar), 5.15 (1H sugar), 4.58 dd (1H sugar), 4.26 m (3H sugar), 4.02 dd (2H sugar), 3.60 t (2H CH=C<u>H</u>$_2$), 1.52 s (3H CH_3), 1.43 s (3H CH_3), 1.32 s (6H CH_3).

14 Compound **1**:

λ max (nm) (ε 10^4.dm^3.$mole^{-1}$.cm^{-1}) CH_2Cl_2: 407 (83.0), 423.5 (287.2), 505 (9.5), 525 (14.2), 596.5 (6.2), 654.5 (4.8).

^1H nmr($CDCl_3$) d ppm: 9.73 m (8H pyrrole), 7.89 d (4H H_4 sugar), 6.75, 6.59, 6.19 m (16H phenyl benzylidene), 6.73 d (4H H_1 sugar), 5.22 d (4H H_2 sugar), 4.90 d (4H, H_3 sugar), 3.75 d, 3.49 d (8H CH_2 benzylidene), 1.90 s, 1.62 s (24H CH_3 isopropylidene), -2.34 s (2H NH).

Compound **2**:

λ max (nm) (ε 10^4.dm^3.$mole^{-1}$.cm^{-1}) CH_2Cl_2: 407 (shoulder) 420 (168), 518 (9.1), 554 (4.7), 603 (5.3), 634 (3.6).

^1H nmr($CDCl_3$) δ ppm: 10.10, 9.57, 9. 23 broad (8H pyrrole), 7.57 m, 7.44 m, 7.18 m (40 H phenyl benzylidene), 5.78 m (8H sugar), 4.97 d (8H CH_2 benzylidene), 4.57 m (12H sugar), 3.60 d (8H CH_2 benzylidene), 1.25 m (24H CH_3 isopropylidene), -2.58 (2H NH)

Compound **3**:

λ max (nm) (ε 10^4.dm^3.$mole^{-1}$.cm^{-1}) CH_2Cl_2: 419 (144), 518 (11.5), 553 (3.3), 591 (4.2), 646 (2.8).

^1H nmr ($CDCl_3$) δ ppm: 9.74 broad (8H pyrrole), 7.7 s (4H H_5 sugar), 6.25 d (4H H_1 sugar), 5.19 d (4H H_4 sugar), 5.14 dd (4H H_3 sugar), 4.76 dd (4H H_2 sugar), 1.87 s, 1.78 s, 1.54 s, 1.19 s (48H CH_3 isopropylidene), -2.97 s (2H NH).

Compound **4**:

λ max (nm) (ε 10^4.dm^3.$mole^{-1}$.cm^{-1}) CH_2Cl_2: 418 (387), 517.5 (19.5), 552.5 (8.9), 594 (9.3), 654 (5.6).

Compound **5**:

λ max (nm) (In relative intensity) CH_2Cl_2: 414 (1), 512 (0.05), 537 (0.02), 588 (0.025), 678 (0.015).

(Received in France 19 August 1992)