Pergamon

Tetrahedron Letters 40 (1999) 3359–3362

TETRAHEDRON LETTERS

Exploitation of an Unexpected *in Situ* Heteroaromatic Bromination for the Synthesis of a Porphyrin Functionalized Nucleoside.

Nathalie Solladié,* Maurice Gross

Laboratoire d'Electrochimie et de Chimie Physique du Corps Solide,
Université Louis Pasteur et CNRS, 4 rue Blaise Pascal, 67070 Strasbourg, France

Received 11 January 1999; accepted 2 March 1999

Abstract: A 2'-deoxyuridine derivative functionalized *via* an acetylenic junction with a Zn(II) tetraarylporphyrin has been prepared. Is also reported an unexpected *in situ* bromination of the uracil nucleic base at the C5 position, which occurs during the transformation of a dibromo-olefin into its corresponding acetylenic anion.

Multiporphyrinic devices attract more and more attention, for the synthesis of artificial light harvesting complexes[1] as well as for the elaboration of photonic and electronic wires.[2] In natural photosynthetic systems, the absorption of a photon by a pigment in the antenna complexes is followed by migration of the excited state among the pool of pigments until the reaction center is reached.[3]
In order to mimic such systems, porphyrin-functionalized oligonucleotides with modified nucleotidic backbone were envisaged. The modifications of the nucleosides and the substituents on the porphyrins can then be chosen to provide a parallel orientation of the porphyrin moieties, as are the chromophores in the natural photosynthetic system. Modeling of a simplified dimer of this type (Figure 1) suggests that it seems reasonable to expect such a conformation.

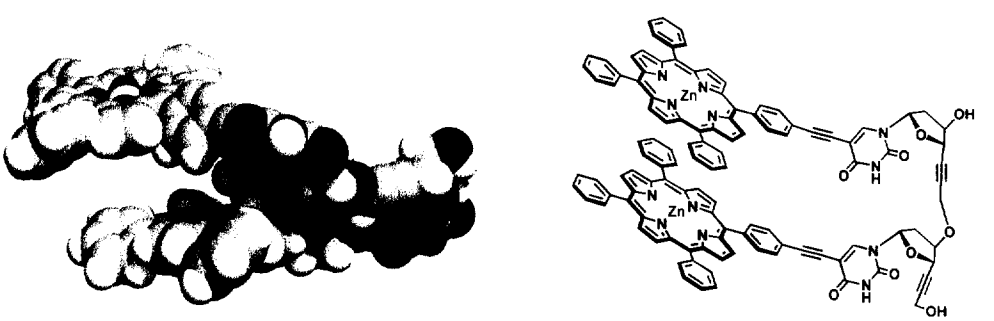


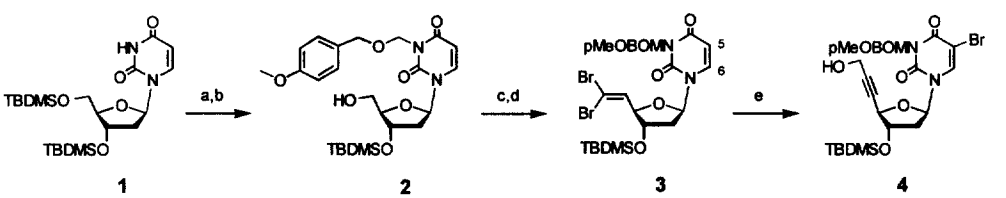
Figure 1. Molecular model of a porphyrin dimer (substituents on the tetraphenylporphyrins have been omitted for clarity).

Fax: 33 388 61 15 53, E-mail: nsolladie@chimie.u-strasbg.fr

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00483-9

The synthesis of such porphyrin-functionalized oligonucleotides, based on the use of monomer **8**,[4] will allow to vary as desired the metallated porphyrins within the oligomers. This would open the route to the elaboration of new photonic or electronic devices. In this paper, the synthesis of the porphyrin/nucleoside hybrid **8** is reported, as well as an unexpected *in situ* bromination of the uracil moiety.

The preparation of compound **8** is depicted in Schemes 1 and 2. The synthesis of the propargylic alcohol **4** started from protected 2'-deoxyuridine **1** which was readily accessible on large scale.[5] Deoxyuridine **1** was protected on the NH group by treatment with *p*-methoxybenzyl chloromethyl ether (pMeOBOMCl) under standard conditions.[6] After selective deprotection of the TBDMS-protected primary alcohol under acidic conditions, the dibromo-olefin **3** was obtained in 60% yield using Swern oxidation followed by the Wittig reaction with $Ph_3P{=}CBr_2$.[7] Treatment of **3** with excess LDA unexpectedly resulted, after quenching with paraformaldehyde, in the brominated propargylic alcohol **4**. In a typical procedure, a solution of 1.06 g of compound **3** (1.64 mmol) in dry THF under argon was treated at –78°C with 1.7 mL of a 2.0 M solution of LDA in THF (3.40 mmol, 2.1 eq.). After 30 min, the cooling bath was removed and a large excess of formaldehyde was added, which necessitated the depolymerization of paraformaldehyde using a blow torch, and the introduction of formaldehyde into the solution via a gas inlet. Despite the repolymerization of a major part of the formaldehyde into the solution, thin layer chromatography showed the reaction was almost complete under such conditions within two hours. The reaction was then quenched with a saturated solution of ammonium chloride. After classical work-up and chromatography on silica gel (ϕ = 2 cm, h = 19 cm, eluent: ethyl acetate/hexane 30/70) the desired brominated propargylic alcohol **4** was obtained in 52% yield. Although the proton NMR spectrum of compound **4** shows the disappearance of proton H(5) and a 0.82 ppm deshielding of proton H(6), the nature of the brominated propargylic alcohol **4** was confirmed by FAB Mass Spectrometry (595.1, $[M+H]^+$, calc. 595.1).[8] Upon treatment with LDA, the dibromo-olefin **3** is converted by halogen/lithium exchange into its corresponding 1-halo-1-lithioalkene. This halocarbenoid then undergoes an hydride shift which resulted in an LiBr elimination, and is thus transformed into a terminal alkyne. If an excess of LDA is used, this alkyne is deprotonated *in situ* and the reaction with an electrophile becomes directly possible.[9] It can be reasonably postulated that during the halogen/lithium exchange which initiates this reaction, the formal "Br^+" cation released is quenched by the nucleic base probably via an aromatic electrophilic substitution. It is worth noting that the 52% yield obtained for the conversion of dibromo-olefin **3** to compound **4** corresponds to a one-pot three-steps process.

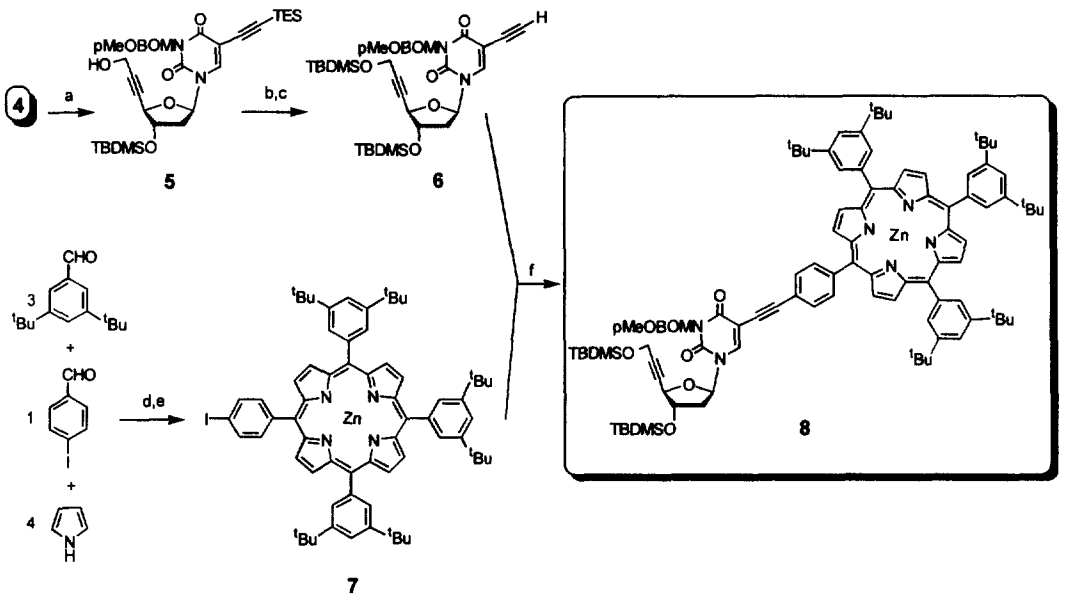


1 2 3 4

Scheme 1. a) pMeBOMCl (1.6 eq.), DBU (4.1 eq.), CH_3CN, 0°C, 2h30, 96%. b) TFA (1.7 eq.), THF/H_2O 3/1, rt, 9h30, 61%. c) Oxalyl chloride (1.6 eq.), DMSO (3.1 eq.), CH_2Cl_2, -78°C, 1h30. d) NEt_3 (6.3 eq.), $Ph_3P{=}CBr_2$ (2.0 eq.), 0°C to rt, 24h. e) LDA (2.1 eq.), THF, -78°C, 30min then $(CH_2O)_n$ (excess), 0°C to rt, 2h, 52%.

The diacetylene **5** (Scheme 2) was synthesized by a palladium-catalyzed coupling involving **4** and triethylsilylacetylene.[10] After protection of the propargylic alcohol under standard conditions, the triethylsilyl group was cleaved with potassium carbonate in a 1/1 mixture of THF/methanol below 10°C. Such a control of the temperature is necessary to limit the formation of a by-product resulting from the addition of methanol to the triple bond substituted by a protected primary alcohol. The condensation of 3,5-di-*tert*-butylbenzaldehyde and *p*-iodobenzaldehyde with pyrrole under Lindsey's conditions[11] gave, after metallation via a standard procedure,[11b] the Zn(II) porphyrin **7**. The synthesis of compound **8**[12] was then

finally achieved in 40% yield by palladium-catalyzed coupling between the terminal alkyne **6** and the iodo-porphyrin **7**.[1b, 13] The non-reacted Zn(II) porphyrin **7** was recovered quantitatively, but it was not possible to isolate any remaining free acetylene **6** which may decompose during the course of the reaction.



Scheme 2. a) HCCTES (3.9 eq.), CuI (0.60 eq.), $Pd(PPh_3)_2Cl_2$ (0.24 eq.), NEt_3, rt, 24h, 86%. b) TBDMSCl (1.3 eq.), imidazole (3.2 eq.), DMF, rt, 18h, 89%. c) K_2CO_3 (4.6 eq.), THF/MeOH 1/1, 3h30 at 0°C and 4h at 10°C, 77%. d) $BF_3.OEt_2$ (1.9 eq.), $CHCl_3$, rt, 1h then chloranil (3.0 eq.), $CHCl_3$, reflux, 1h, 5%. e) $Zn(OAc)_2.2H_2O$ (1.9 eq.), $CHCl_3$, reflux, 1h30, 91%. f) CuI (0.86 eq.), $Pd(PPh_3)_2Cl_2$ (0.47 eq.), NEt_3, rt, 24h, 40%.

A more convergent route has been tried through the reaction of 1 equivalent of compound **4** and 1.1 equivalent of 5-(4-ethynylphenyl)-10,15,20-tris(di-*tert*-butylphenyl)porphyrin with $Pd(PPh_3)Cl_2$ and copper iodide in refluxing deoxygenated triethylamine under argon.[11b,14] The 4,4'-bis[zinc(II)-5,10,15-tris(di-*tert*-butylphenyl)-20-porphyrinyl]diphenylbutadiyne, resulting from a homocoupling reaction, was obtained in 75% yield,[10a] but no desired product could be detected.

An unexpected regioselective *in situ* bromination of the nucleic base of a 2'-deoxyuridine derivative is described in this paper. It occurs at the C5 position of the uracil moiety during the transformation of the dibromo-olefin **3** to its corresponding acetylenic anion. Advantage was taken of this reaction for the further synthesis of a nucleoside/porphyrin hybrid. Functionalizing with a porphyrin the nucleic base of a 2'-deoxyuridine derivative *via* a palladium-catalyzed coupling will allow the easy preparation of many analogs of monomer **8** depending on the nature of the metallated porphyrin involved in the coupling reaction. Such a strategy opens the route to the synthesis of functionalized oligomers in which the sequence of metallated porphyrins can be chosen as desired, and thus to the possible elaboration of new photonic or electronic wires.

Acknowledgements: We thank Nicolas Rieger for the synthesis of porphyrin **7**, Raymond Hueber and Dr. A. Van Dorsselaer for the mass spectrometry measurements.

References and Notes

1. a) Prathapan, S.; Johnson, T. E.; Lindsey, J. S.; *J. Am. Chem. Soc.* **1993**, *115*, 7519-7520; b) Wagner, R. W.; Johnson, T. E.; Lindsey, J. S.; *J. Am. Chem. Soc.* **1996**, *118*, 11166-11180 and references cited therein; c) Officer, D. L.; Burrell, A. K.; Reid, D. C. W.; *J. Chem. Soc., Chem. Commun.* **1996**, 1657-1658; d) Vollmer, M. S.; Würthner, F.; Effenberger, F.; Emele, P.; Meyer, D. U.; Stümpfig, T.; Port, H.; Wolf, H. C.; *Chem. Eur. J.* **1998**, *4*, 260-269.
2. a) Wagner, R. W.; Lindsey, J. S.; *J. Am. Chem. Soc.* **1994**, *116*, 9759-9760 and references cited therein; b) Crossley, M. J.; Burn, P. L.; Langford, S. J.; Prashar, J. K.; *J. Chem. Soc., Chem. Commun.* **1995**, 1921-1923; c) Wagner, R. W.; Lindsey, J. S.; Seth, J.; Palaniappan, V.; Bocian, D. F.; *J. Am. Chem. Soc.* **1996**, *118*, 3996-3997; d) Osuka, A.; Shimidzu, H.; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 135-137.
3. a) Barber, J.; Andersson, B.; *Nature* **1994**, *370*, 31-34; b) Kühlbrandt, W.; *Nature* **1995**, *374*, 497-498; c) McDermott, G.; Prince, S. M.; Freer, A. A.; Hawthornthwaite-Lawless, A. M.; Papiz, M. Z.; Cogdell, R. J.; Isaacs, N. W.; *Nature* **1995**, *374*, 517-521; d) Pullerits, T.; Sundström, V.; *Acc. Chem. Res.* **1996**, *29*, 381-389.
4. A porphyrin/nucleoside hybrid has been previously reported for the study of photoinduced electron transfer by self-assembly with a quinone moiety. a) Sessler, J. L.; Wang, B.; Harriman, A.; *J. Am. Chem. Soc.* **1993**, *115*, 10418-10419; b) Berman, A.; Izraeli, E. S.; Levanon, H.; Wang, B.; Sessler, J. L.; *J. Am. Chem. Soc.* **1995**, *117*, 8252-8257.
5. Armstrong, R. W.; Gupta, S.; Whelihan, F.; *Tetrahedron Lett.* **1989**, *30*, 2057-2060.
6. Wendeborn, S.; Jouanno, C.; Wolf, R. M.; De Mesmaeker, A.; *Tetrahedron Lett.* **1996**, *37*, 5511-5514.
   For the preparation of pMeOBOMCl see: a) Corey, E. J.; Bock, M. G.; *Tetrahedron Lett.* **1975**, 3269-3270; b) Benneche, T.; Strande, P.; Undheim, K.; *Synthesis* **1983**, 762-763.
7. a) Lebreton, J.; De Mesmaeker, A.; Waldner, A.; *Synlett* **1994**, 54-56; b) Anthony, J.; Boldi, A. M.; Rubin, Y.; Hobi, M.; Gramlich, V.; Knobler, C. B.; Seiler, P.; Diederich, F.; *Helv. Chim. Acta* **1995**, *78*, 13-45.
8. Selected spectroscopic data for **4**: ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.12 (s, 6 H), 0.91 (s, 9 H), 1.83 (t, J = 5.0, 1 H), 2.15 (ddd, J = 13.5, J = 4.5, J = 7.5, 1 H), 2.56 (dd, J = 13.5, J = 6.0, 1 H), 3.80 (s, 3 H), 4.39 (d, J = 4.0, 2 H), 4.49 (d, J = 4.0, 1 H), 4.64 (s, 2 H), 4.68 (s, 1 H), 5.49 (s, 2 H), 6.34 (dd, J = 7.5, J = 6.0, 1 H), 6.87 (d, J = 8.5, 2 H), 7.31 (d, J = 8.5, 2 H), 8.11 (s, 1 H); MS (FAB^+): *m/z* = 595.1 ($[M+H]^+$, calc. 595.1).
9. Braun, M.; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 430-451 and references cited therein.
10. a) Cai, C.; Vasella, A.; *Helv. Chim. Acta* **1995**, *78*, 2053-2064; b) Hobbs, F. W. Jr.; *J. Org. Chem.* **1989**, *54*, 3420-3422; c) Sessler, J. L.; Wang, R.; *J. Am. Chem. Soc.* **1996**, *118*, 9808-9809; d) Hurley, D. J.; Tor, Y.; *J. Am. Chem. Soc.* **1998**, *120*, 2194-2195.
11. a) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M.; *J. Org. Chem.* **1987**, *52*, 827-836; b) Lindsey, J. S.; Prathapan, S.; Johnson, T. E.; Wagner, R. W.; *Tetrahedron* **1994**, *50*, 8941-8968.
12. Selected spectroscopic data for **8**: UV-VIS λ_{max} (CH_2Cl_2)/nm: 424 (387000), 552 (17400), 593 (6300); ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.17 (s, 6 H), 0.18 (s, 6 H), 0.93 (s, 9 H), 0.95 (s, 9 H), 1.53 (s, 18 H), 1.54 (s, 36 H), 2.25 (ddd, J = 14.0, J = 4.5, J = 7.5, 1 H), 2.62 (dd, J = 13.5, J = 6.0, 1 H), 3.83 (s, 3 H), ~4.56 (hidden, 1 H), 4.56 (d, J = 1.5, 2 H), 4.73 (s, 2 H), 4.76 (s, 1 H), 5.57 (s, 2 H), 6.43 (dd, J = 7.0, J = 6.0, 1 H), 6.92 (d, J = 8.5, 2 H), 7.40 (d, J = 8.5, 2 H), 7.80 and 7.81 (2t, J = 2.0, 3 H), 7.92 (d, J = 8.5, 2 H), 8.09 and 8.10 (2d, J = 2.0, 6 H), 8.22 (d, J = 8.5, 2 H), 8.24 (s, 1 H), 8.93 (d, J = 4.5, 2 H), 9.02 (s, 4 H), 9.02 (d, J = 4.5, 2 H)); ^{13}C-NMR ($CDCl_3$, 50 MHz): -5.05, -4.83, 18.02, 25.68, 25.80, 31.74, 35.03, 41.71, 51.64, 55.30, 70.61, 72.08, 77.95, 80.96, 81.76, 88.55, 93.25, 99.82, 113.77, 119.61, 120.80, 121.85, 122.55, 122.76, 129.54, 129.60, 129.66, 129.87, 131.36, 132.20, 132.31, 132.44, 134.29, 135.09, 135.21, 141.34, 141.75, 143.51, 148.52, 149.68, 150.03, 150.40, 150.50, 159.32, 161.42; MS (FAB^+): *m/z* = 1668.2 ($[M+H]^+$, calc. 1668.7).
13. Vidal-Ferran, A.; Müller, C. M.; Sanders, J. K. M.; *J. Chem. Soc., Chem. Commun.* **1994**, 2657-2658.
14. a) Taylor, P. N.; Wylie, A. P.; Huuskonen, J.; Anderson, H. L.; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 986-989; b) Jiang, B.; Yang, S.-W.; Barbini, D. C.; Jones, W. E. Jr.; *J. Chem. Soc., Chem. Commun.* **1998**, 213-214.