COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Synthesis and Bergman cyclization of a β-extended porphyrenediyne†

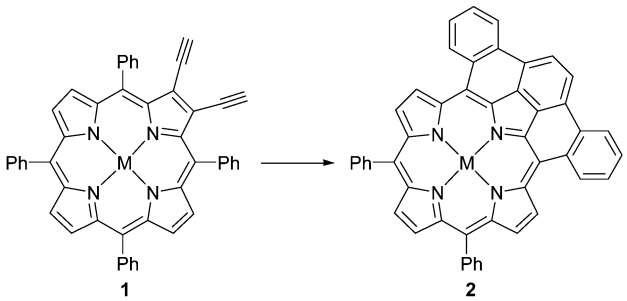
John D. Spence,* Eric D. Cline, Domingo M. LLagostera and Patrick S. O'Toole
Trinity University, Department of Chemistry, One Trinity Place, San Antonio, TX, 78212, USA.
E-mail: john.spence@trinity.edu; Fax: +1-210-999-7569; Tel: +1-210-999-7660

Received (in Corvallis, OR, USA) 30th September 2003, Accepted 12th November 2003
First published as an Advance Article on the web 9th December 2003

Condensation of a porphyrin-2,3-dione with a 1,2-diaminoarenediyne affords a β-extended porphyrinic-enediyne: upon thermal Bergman cyclization the quinoxaline spacer positioned between the macrocycle and the enediyne prevents tandem radical cyclization to a picenoporphyrin.

The Bergman cyclization[1] of *cis*-1,5-diyne-3-enes to produce 1,4-phenyl diradicals is an attractive mode of action for the destruction of biological targets. Enediyne antitumor antibiotics utilize their complex molecular architecture to control the delivery and activation of cyclic enediynes to bind and ultimately cleave DNA leading to their potent cytotoxicity.[2] Use of these natural products, however, is limited by a lack of tumor cell selectivity and their long term toxicity. Conjugation of a porphyrin macrocycle to an enediyne pro-drug can provide an improved delivery system with enhanced pharmacokinetic properties. In particular, the development of cationic porphyrins as sensitizers for photodynamic therapy[3] has led to the design of macrocycles that display modest tumor selectivity and bind to DNA[4] and proteins like bovine serum albumin[5] making them ideal delivery vehicles for enediynes.

The first example of a porphyrin-annulated enediyne was reported by Smith *et al*. who prepared Ni(II) 2,3-dialkynyl-5,10,15,20-tetraphenylporphyrin.[6] Upon thermal cyclization the 1,4-didehydrobenzene intermediate undergoes a tandem radical cyclization[7] with the neighboring *meso*-phenyl substituents followed by dehydrogenation to afford highly conjugated macrocycles referred to as picenoporphyrins (Scheme 1). Further studies by Zaleski *et al*. revealed that this cascade event can occur at room temperature in the presence of DDQ indicating that the dehydrogenation step is rate limiting.[8] In the absence of DDQ the reaction temperature, as measured by DSC, is influenced by both steric[8] and electronic factors.[9] The accelerated reactivity of these acyclic enediynes may be similar to the enhanced rate of cyclization of *ortho*-substituted arenediynes operating by steric assistance.[10] Extension of this methodology to octaalkynylporphyrins results in significant exotherms indicative of Bergman cyclization in DSC studies, however, thermal and photochemical solution cyclizations lead to reduction of the porphyrin macrocycle.[11]



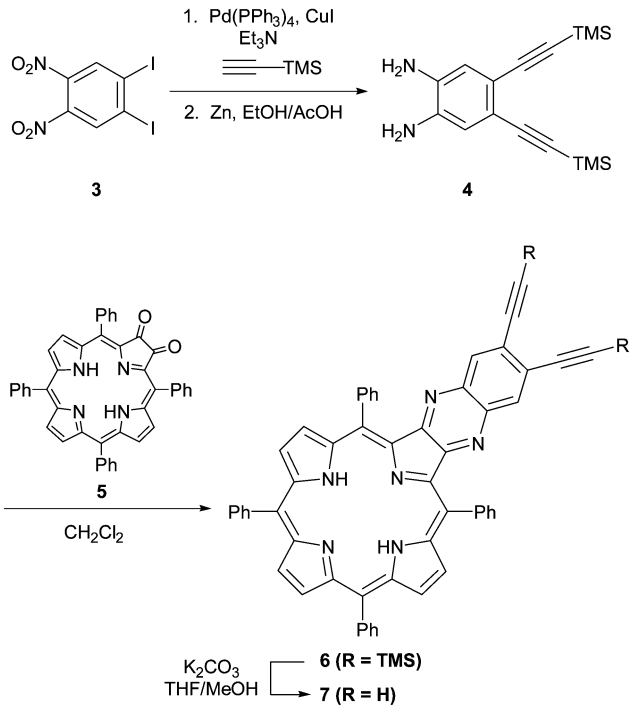
Scheme 1 Tandem radical cyclization of 2,3-dialkynylporphyrins.

To prevent participation of the *meso*-phenyl substituents in the reaction pathway we have prepared a porphyrenediyne that contains a conjugated spacer between the enediyne core and the porphyrin macrocycle. The presence of this spacer displaces the enediyne away from the porphyrin and removes the enediyne alkene from the aromatic pathway of the macrocycle. As a result the enediyne can react as a typical arenediyne and avoid alternative reaction pathways, such as tandem radical cyclization and macrocycle reduction, previously observed for porphyrinic-enediynes.

We have employed the well established condensation of porphyrin-2,3-diones with aromatic diamines as a rapid entry to porphyrins containing β-fused enediyne units.[12] This strategy simultaneously incorporates a quinoxaline spacer between the porphyrin and the enediyne core preventing tandem radical cyclization to a picenoporphyrin.

The synthesis of a 1,2-diaminoarenediyne and resulting condensation with a porphyrin-2,3-dione to produce the porphyrenediyne is outlined in Scheme 2. Di-iodination of 1,2-dinitrobenzene readily affords 1,2-diiodo-4,5-dinitrobenzene **3**.[13] Subsequent coupling with two equivalents of trimethylsilylacetylene followed by reduction with Zn in 5% acetic acid–ethanol gives diamine **4** in 62% yield. Condensation of **4** with free-base porphyrin-2,3-dione **5**[14] in CH_2Cl_2 then gives porphyrenediyne **6** in 90% yield. To facilitate Bergman cyclization the trimethylsilyl groups are removed by stirring with K_2CO_3 in THF–MeOH to afford a 90% yield of porphyrenediyne **7**.‡

The structure of **7** is evident from its ^{1}H NMR spectrum which displays C_{2v} symmetry similar to dione **5** with the presence of a new aromatic 2H singlet at δ 8.05 and a 2H singlet at δ 3.52 due to



Scheme 2 Synthesis of β-extended porphyrenediyne **7**.

† Electronic Supplementary Information (ESI) available: experimental details for the synthesis of compounds **7** and **8**; ^{1}H and ^{13}C NMR spectra of **7** and **8**. See http://www.rsc.org/suppdata/cc/b3/b312001e

DOI: 10.1039/b312001e

acetylenic hydrogens in $CDCl_3$. The ^{13}C NMR spectrum further confirms the molecular symmetry with 23 signals and the UV-Vis spectrum of **7** is characteristic of porphyrins containing an exocyclic ring with a strong Soret band at 421 nm along with Q bands at 531, 602 and 652 nm that are slightly red-shifted compared to tetraphenylporphyrin.

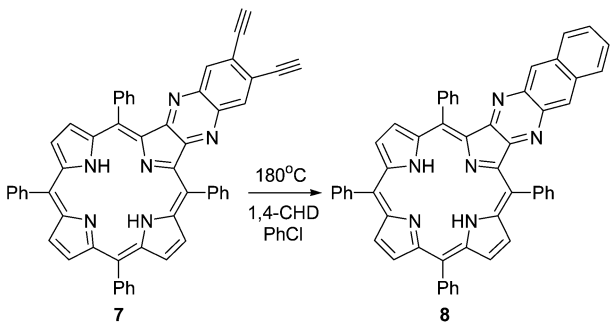
In contrast to the room temperature cyclization of 2,3-dialkynylporphyrins stirring a solution of **7** in $CHCl_3$–MeOH in the presence of DDQ does not promote cyclization. Similarly, heating a solution of **7** up to 110 °C for several hours shows no evidence of a cyclized product. In each case unreacted starting material is obtained as the only isolated porphyrinoid product.

The cyclization of porphyrenediyne **7** can be effected at higher temperatures in the presence of 1,4-cyclohexadiene (1,4-CHD) to afford adduct **8** in 92% yield (Scheme 3). The high reaction temperatures for the cyclization of **7**, requiring heating at 180 °C for 24 hours, is likely due to annulation to the aromatic quinoxalinoporphyrin resulting in the reversibility of the Bergman cyclization. Supporting this, the reaction time was found to be dependent upon the concentration of 1,4-CHD indicating that hydrogen atom abstraction is rate limiting as previously observed for arenediynes.[15]

The structure of compound **8** was confirmed by ^1H NMR spectroscopy by the disappearance of the terminal alkyne protons present in **7** along with the appearance of two new aromatic multiplets centered at δ 7.56 and 8.15. The ^{13}C NMR spectrum further confirmed the structure of **8** displaying the anticipated 23 aromatic carbon resonances while the UV-Vis spectrum contains a strong Soret band at 427 nm along with Q bands at 533, 607 and 660 nm that are red shifted compared to **6** and **7** as a result of increased conjugation.

Photochemical activation of porphyrenediyne **7** under a variety of conditions, however, results in recovery of unreacted starting material using isopropanol or 1,4-CHD as the hydrogen atom donor. This result is not surprising as there are no literature examples describing photocyclization of terminal enediynes such as **7**.

The design of a porphyrenediyne that undergoes a traditional Bergman cyclization has potential for the development of pro-drugs that utilize the macrocycle to facilitate delivery and activation of the enediyne. Kinetic studies along with alkyne functionalization, including phenylethynyl and cyclic derivatives for improved photochemical activation, are currently under investigation.



7 **8**

Scheme 3 Bergman cyclization of porphyrenediyne **7**.

This work was supported by the Research Corporation (CC5242), the Robert Welch Foundation and the Merck/AAAS Undergraduate Science Research Program.

Notes and references

‡ *Selected data.* **7**: $\delta_H(CDCl_3)$ −2.59 (2H, br s), 3.52 (2H, s), 7.73–7.79 (10H, m), 7.90 (2H, t, *J* 7.4), 8.05 (2H, s), 8.12 (4H, d, *J* 7.3), 8.21 (4H, d, *J* 7.3), 8.72 (2H, s), 8.93 (2H, d, *J* 4.9), 8.96 (2H, d, *J* 4.9). $\delta_C(CDCl_3)$ 81.6, 82.7, 117.3, 121.8, 124.5, 126.8, 126.9, 127.8, 127.9, 128.1, 128.3, 133.8, 134.3, 134.5, 135.3, 138.1, 139.5, 140.0, 141.5, 141.7, 144.9, 153.2, 155.1. $\lambda_{max}(CH_2Cl_2)$ (log ε)/nm 421 (5.27), 531 (4.23), 602 (4.05), 652 (3.31). λ_{max}(TFA–CH_2Cl_2) (log ε)/nm 466 (5.20), 483 (5.22), 605 (3.93), 699 (4.56). HRMS (FAB): calcd for $C_{54}H_{33}N_6$ (MH^+), 765.2767. Found 765.2770. **8**: $\delta_H(CDCl_3)$ −2.43 (2H, br s), 7.56 (2H, dd, *J* 6.7, 3.0), 7.74–7.85 (10H, m), 7.95 (2H, t, *J* 7.6), 8.15 (2H, dd, *J* 6.4, 3.4), 8.18–8.23 (8H, m), 8.47 (2H, s), 8.69 (2H, s), 8.91 (2H, d, *J* 4.4), 8.94 (2H, d, *J* 5.0). $\delta_C(CDCl_3)$ 116.4, 121.9, 126.2, 126.8, 127.0, 127.7, 127.8, 127.9, 128.0, 128.5, 128.8, 133.7, 133.9, 134.0, 134.4, 137.7, 137.8, 139.8, 141.8, 141.9, 146.1, 153.3, 154.8. $\lambda_{max}(CH_2Cl_2)$ (log ε)/nm 426 (5.34), 533 (4.58), 608 (4.36), 660 (3.98). λ_{max}(TFA–CH_2Cl_2) (log ε)/nm 422 (4.99), 459 (5.17), 503 (4.95), 626 (4.40), 711 (4.63). HRMS (FAB): calcd for $C_{54}H_{35}N_6$ (MH^+), 767.2923. Found 767.2921.

1 R. G. Bergman, *Acc. Chem. Res.*, 1973, **6**, 25.
2 A. L. Smith and K. C. Nicolaou, *J. Med. Chem.*, 1996, **39**, 2103; K. C. Nicolaou and W. M. Dai, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1387.
3 E. D. Sternberg, D. Dolphin and C. Bruckner, *Tetrahedron*, 1998, **54**, 4151; R. W. Boyle and D. Dolphin, *Photochem. Photobiol.*, 1996, **64**, 469.
4 H. Ogoshi, T. Mizutani, T. Hayashi and Y. Kuroda, in *The Porphyrin Handbook*, ed. K. M. Kadish, K. M. Smith and R. Guilard, Academic Press, San Diego, 2000, **Vol. 6**, p. 304.
5 A. Bordbar, S. Tangestaninejad and A. Eslami, *J. Biochem. Mol. Biol. Biophys.*, 2001, **5**, 143.
6 H. Aihara, L. Jaquinod, D. J. Nurco and K. M. Smith, *Angew. Chem., Int. Ed.*, 2001, **40**, 3439.
7 J. W. Grissom and T. L. Calkins, *J. Org. Chem.*, 1993, **58**, 5422.
8 M. Nath, J. C. Huffman and J. M. Zaleski, *Chem. Commun.*, 2003, 858.
9 M. Nath, J. C. Huffman and J. M. Zaleski, *J. Am. Chem. Soc.*, 2003, **125**, 11484.
10 I. V. Alabugin, M. Manoharan and S. V. Kovalenko, *Org. Lett.*, 2002, **4**, 1119.
11 T. Chandra, B. J. Kraft, J. C. Huffman and J. M. Zaleski, *Inorg. Chem.*, 2003, **42**, 5158.
12 M. J. Crossley and P. L. Burn, *J. Chem. Soc., Chem. Commun.*, 1987, 39.
13 J. Arotsky, R. Butler and A. C. Darby, *J. Chem. Soc. C*, 1970, 1480.
14 M. J. Crossley and L. G. King, *J. Chem. Soc., Chem. Commun.*, 1984, 920.
15 S. Koseki, Y. Fujimura and M. Hirama, *J. Phys. Chem. A*, 1999, **103**, 7672; T. Kaneko, M. Takahashi and M. Hirama, *Tetrahedron Lett.*, 1999, **40**, 2015.