ORGANIC LETTERS

2007
Vol. 9, No. 25
5291−5294

# Multigram Synthesis of a Water-Soluble Porphyrazine and Derived *seco*-Porphyrazine Labeling Agents

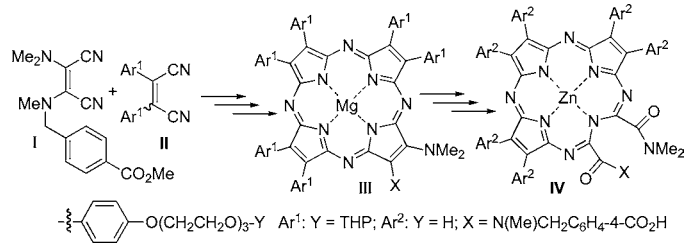
**Xavier Guinchard,[†] Matthew J. Fuchter,[†] Andrea Ruggiero,[†] Brian J. Duckworth,[†] Anthony G. M. Barrett,*[†,] and Brian M. Hoffman*[,‡]**

*Department of Chemistry, Imperial College London, London SW7 2AZ, England, and Department of Chemistry, Northwestern University, Evanston, Illinois 60208*

*agm.barrett@imperial.ac.uk*

**Received October 11, 2007**

## ABSTRACT




**Porphyrazine III has been synthesized on a large scale (18.4 g), with minimal chromatographic purification by employing a novel one-pot, 3-step sequence. Two dinitrile precursors I and II, the latter of which consisted of a mixture of geometric isomers, were transformed, via the corresponding pyrroline diimines, into a mixture of III and the octa-Ar[1]-porphyrazine. Isolated macrocycle III was subsequently transformed into IV, a water-soluble *seco*-porphyrazine suitable for the labeling of biological vectors.**

Photodynamic therapy[1] (PDT) is a noninvasive cancer treatment that uses a combination of visible light and a photosensitizing drug.[2] Following internalization of the photosensitizer in tumor cells, irradiation generates localized singlet oxygen, which may destroy the cancer.[3,4] Suitable photosensitizers for PDT include both porphyrins[5] and tetraazaporphyrins; the former class incorporates Photofrin, the first approved photochemical drug used for cancer therapy.[3] Porphyrins and tetraazaporphyrins are topologically related and differ by only the presence of *meso*-nitrogen atoms within the ligand framework. Tetraazaporphyrins can be further divided into phthalocyanines[6] and porphyrazines[7] (Pz). Vicinal diaminoporphyrazines readily undergo oxidative ring scission of the $R_2NC{=}CNR_2$ unit to provide the corresponding *seco*-porphyrazines. These macrocyclic compounds, as well as porphyrazines in general, may be of use

[†] Imperial College London.
[‡] Northwestern University.

(1) For general literature on PDT, see: Dougherty, T. J.; Levy, J. G. In *CRC Handbook of Organic Photochemistry and Photobiology*, 2nd ed.; Horspool, W., Lenci, F., Eds.; CRC Press: Boca Raton, FL, 2004; pp 147/117−147/141.

(2) For general applications of optical agents in detection of tumors, see: (a) Jiang, H.; Iftimia, N. V.; Xu, Y.; Eggert, J. A.; Fajardo, L. L.; Klove, K. L. *Acad. Radiol.* **2002**, *9*, 186. (b) Weissleder, R.; Ntziachristos, V. *Nat. Med.* **2003**, *9*, 123. (c) Sevick-Muraca, E. M.; Godavarty, A.; Houston, J. P.; Thompson, A. B.; Roy, R. In *Handbook of Biomedical Fluorescence*; Pogue, B.W., Mycek, M., Eds.; Marcel Dekker:New York, 2003; pp 445−527.

(3) For general applications of optical agents on treatment of tumors, see: (a) Kessel, D.; Dougherty, T. J. *Rev. Contemp. Pharmacother.* **1999**, *10*, 19. (b) Bonnett, R. *Rev. Contemp. Pharmacother.* **1999**, *10*, 1. (c) Dolmans, D. E. J. G. J.; Fukumura, D.; Jain, R. K. *Nat. Rev. Cancer* **2003**, *3*, 380. (d) Jori, G. In CRC *Handbook of Organic Photochemistry and Photobiology*, 2nd ed.; Horspool, W., Lenci, F., Eds.; CRC Press: Boca Raton, FL, 2004; pp 146/110−146/141.

(4) Brown, S. B.; Brown, E. A.; Walker, I. *Lancet Oncol.* **2004**, *5*, 497.

(5) *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978−1979; Vols. 1−7.

(6) *Phthalocyanines*: *Properties and Applications*; Leznoff, C. C., Lever, A. B. P., Eds.; VCH Publishers: Weinheim, Germany, 1989−1996; Vols. 1−4.

(7) (a) Michel, S. L. J.; Hoffman, B. M.; Baum, S. V.; Barrett, A. G. M. Peripherally-Functionalized Porphyrazines: Novel Metallomacrocycles with Broad, Untapped Potential. In *Progress in Inorganic Chemistry*; Karlin, K. D., Ed.; J. Wiley and Sons: New York, 2001; p 473. (b) Montalban, A. G.; Baum, S. M.; Barrett, A. G. M.; Hoffman, B. M. *J. Chem. Soc., Dalton Trans.* **2003**, 2093.

10.1021/ol702481x CCC: $37.00 
**Published on Web 11/15/2007**

for PDT and biomedical optical imaging[8] due to their intense Q-band in the UV−vis spectrum and, in many cases, excellent singlet oxygen quantum yield[9] on photosensitization.

While a number of procedures have been developed recently for the synthesis of metalated and free-base porphyrazines,[10] the magnesium ion-templated Linstead macrocyclization[11] of acyclic maleonitriles is still the most widely used method for the preparation of these macrocycles. For the synthesis of unsymmetrical porphyrazines, the statistical co-macrocyclization of two different (*Z*)-dinitriles (represented by A and B) is currently the only viable method for their synthesis. This procedure results in the formation of a mixture of porphyrazines $A_4Pz$, $A_3BPz$, both *cis*- and *trans*-$A_2B_2Pz$, $AB_3Pz$, and $B_4Pz$, the ratios of which depend on the ratios of the precursor dinitriles A and B. Such reactions are frequently plagued with poor yields and difficulties with purification. Previously, we have used a ROM-polymerization-capture release strategy to tackle this shortcoming.[12] In this paper, we wish to describe the multigram scale synthesis of an $A_3B$ porphyrazine **15** and its application to the synthesis of the *seco*-porphyrazine **1** (Figure 1), a current candidate

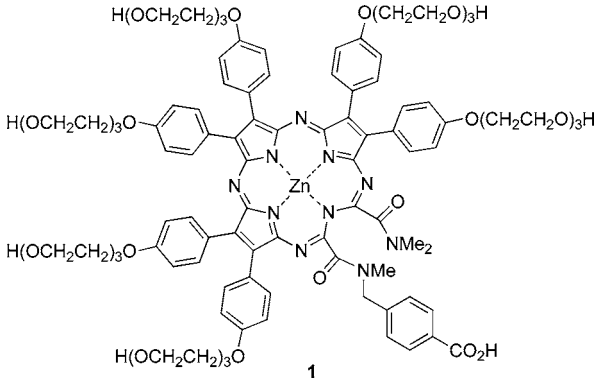
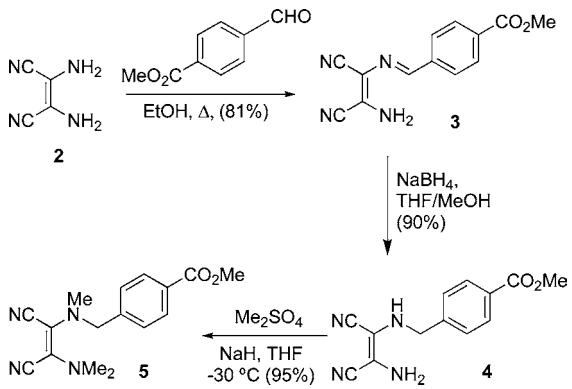



**Figure 1.** *seco*-Porphyrazine photosensitizer.

for PDT studies. Photosensitizer **1** possesses (i) polyethylene glycol chains, to enhance water solubility and facilitate the internalization of dye in cells, (ii) a carboxylic acid moiety, used for bioconjugation,[13] and (iii) the *seco* functionality, which provides high singlet oxygen quantum yields.[9] We now report an efficient, concise chromatography-minimized synthesis via Linstead macrocyclization of pyrroline diimines.

Utilizing the protocol of Sheppard and co-workers, maleonitrile **5** was prepared in three steps from commercially available diaminomaleonitrile **2** (Scheme 1).[14] Heating ma-

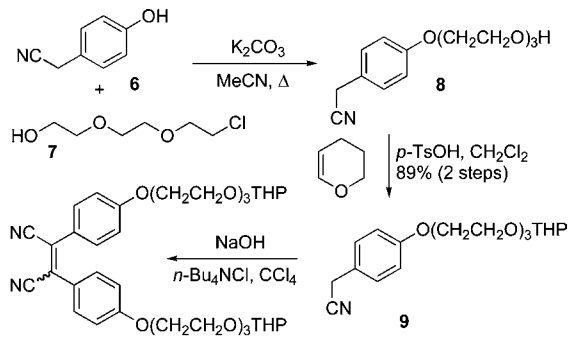
**Scheme 1**




leonitrile **2** in ethanol in the presence of methyl 4-formylbenzoate yielded the imine **3**, which was reduced with sodium borohydride in THF and methanol to give the amine **4** in 73% yield over the two steps. Subsequent methylation with dimethyl sulfate gave maleonitrile **5** in 95% yield.

Maleonitrile **10** was prepared from phenol **6** by alkylation with chloride **7** to give the alcohol **8** in quantitative yield (Scheme 2). Following protection of **8** by dihydropyran to

**Scheme 2**




***Z*-10**: 36%
***E*-10**: 38%
***Z,E*-10** (no separation): 83%

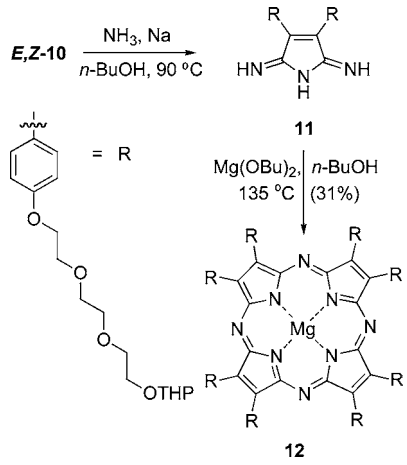
give **9**, oxidative coupling with carbon tetrachloride under basic conditions[15] gave a mixture of maleonitrile ***Z*-10** and

(8) Hammer, N. D.; Lee, S.; Vesper, B. J.; Elseth, K. M.; Hoffman, B. M.; Barrett, A. G. M.; Radosevich, J. A. *J. Med. Chem.* **2005**, *48*, 8125.
(9) (a) Andersen, K.; Anderson, M.; Anderson, O. P.; Baum, S.; Baumann, T. F.; Beall, L. S.; Broderick, W. E.; Cook, A. S.; Eichhorn, D. M.; Goldberg, D.; Hope, H.; Jarrell, W.; Lange, S. J.; McCubbin, Q. J.; Mani, N. S.; Miller, T.; Montalban, A. G.; Rodriguez-Morgade, M. S.; Lee, S.; Nie, H.; Olmstead, M. M.; Sabat, M.; Sibert, J. W.; Stern, C.; White, A. J. P.; Williams, D. B. G.; Williams, D. J.; Barrett, A. G. M.; Hoffmann, B. M. *J. Heterocycl. Chem.* **1998**, *35*, 1013. (b) Mani, N. S.; Beall, L. S.; White, A. J. P.; Williams, D. J.; Barrett, A. G. M.; Hoffman, B. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1943. (c) Montalban, A. G.; Lange, S. J.; Beall, L. S.; Mani, N. S.; Williams, D. J.; White, A. J. P.; Barrett, A. G. M.; Hoffman, B. M. *J. Org. Chem.* **1997**, *62*, 9284. (d) Sakellariou, E. G.; Montalban, A. G.; Meunier, H. G.; Ostler, R. B.; Rumbles, G.; Barrett, A. G. M.; Hoffman, B. M. *J. Photochem. Photobiol. A: Chem.* **2000**, *136*, 185.
(10) (a) Giribabu, L.; Chandrasekharam, M.; Mohan, S. M.; Rao, C. S.; Kantam, M. L.; Reddy, M. R.; Reddy, P. Y.; Toru, T. *Synlett* **2006**, 1604. (b) Chandrasekharam, M.; Srinivasa Rao, C.; Surya, P. S.; Lakshmi Kantam, M.; Ramesh Reddy, M.; Yella Reddy, P.; Toru, T. *Tetrahedron Lett.* **2007**, *48*, 2627. (c) Donzello, M. P.; Dini, D.; D'Arcangelo, G.; Ercolani, C.; Zhan, R.; Ou, Z.; Stuzhin, P. A.; Kadish, K. M. *J. Am. Chem. Soc.* **2003**, *125*, 14190.
(11) Linstead, R. P.; Whalley, M. *J. Chem Soc.* **1952**, 4839.
(12) (a) Fuchter, M. J.; Vesper, B. J.; Murphy, K. A.; Collins, H. A.; Philips, D.; Hoffman, B. M.; Barrett, A. G. M. *J. Org. Chem.* **2005**, *70*, 2793. (b) Fuchter, M. J.; Hoffman, B. M.; Barrett, A. G. M. *J. Org. Chem.* **2005**, *70*, 5086.

fumaronitrile ***E*-10** isolated in 36% and 38% yields, respectively, by chromatography on silica gel. In our hands, however, this separation could not be easily performed on more than a 5 g scale since larger scale separations resulted in partial THP-deprotection and/or degradation. These difficulties were avoided by using the mixture of geometric isomers directly in the next step without separation. It is noteworthy that this three-step sequence could be performed on a 100 g scale of the starting phenol **6** to provide the mixture of dinitriles ***E*,*Z*-10** in 83% (150 g) overall yield.

As an initial approach to the $A_3B$ porphyrazine, dinitriles **5** and ***Z*-10** (1:6 ratio) were co-macrocyclized under Linstead conditions[11] by reflux in *n*-butanol in the presence of freshly prepared magnesium butoxide to give the desired transesterified $A_3BPz$ **14**, along with the symmetrical $A_4Pz$ **12**. Chromatography on silica gel gave pure $A_3B$ **14** in 36% isolated yield. This method of purification on quantities larger than 500 mg, however, is prohibitively time-consuming due to the high polarity and strong aggregation of the macrocycles. We consequently sought to develop another strategy to allow the scale-up of this synthesis. Importantly, any such procedure would ideally utilize both ***E*-** and ***Z*-10** as their separation is an obvious bottleneck in the synthetic sequence. It has been reported that Linstead macrocyclization can be performed with not only *Z*-dinitriles but also pyrroline diimines. These latter compounds may be considered as analogues of the initial intermediates in Linstead macrocyclization, and can be obtained by reaction of a dinitrile with ammonia in the presence of a catalytic amount of sodium in ethylene glycol.[16] Under these reaction conditions, isomerization of either the dinitrile or a subsequent reaction intermediate occurs meaning both *Z* and *E* dinitriles yield the corresponding, geometrically locked, pyrroline diimine. Indeed, the reaction of the mixture of dinitriles ***E*,*Z*-10** with ammonia in *n*-butanol or ethylene glycol, at 100 °C, afforded the corresponding pyrroline diimine **11** (Scheme 3). This

**Scheme 3**



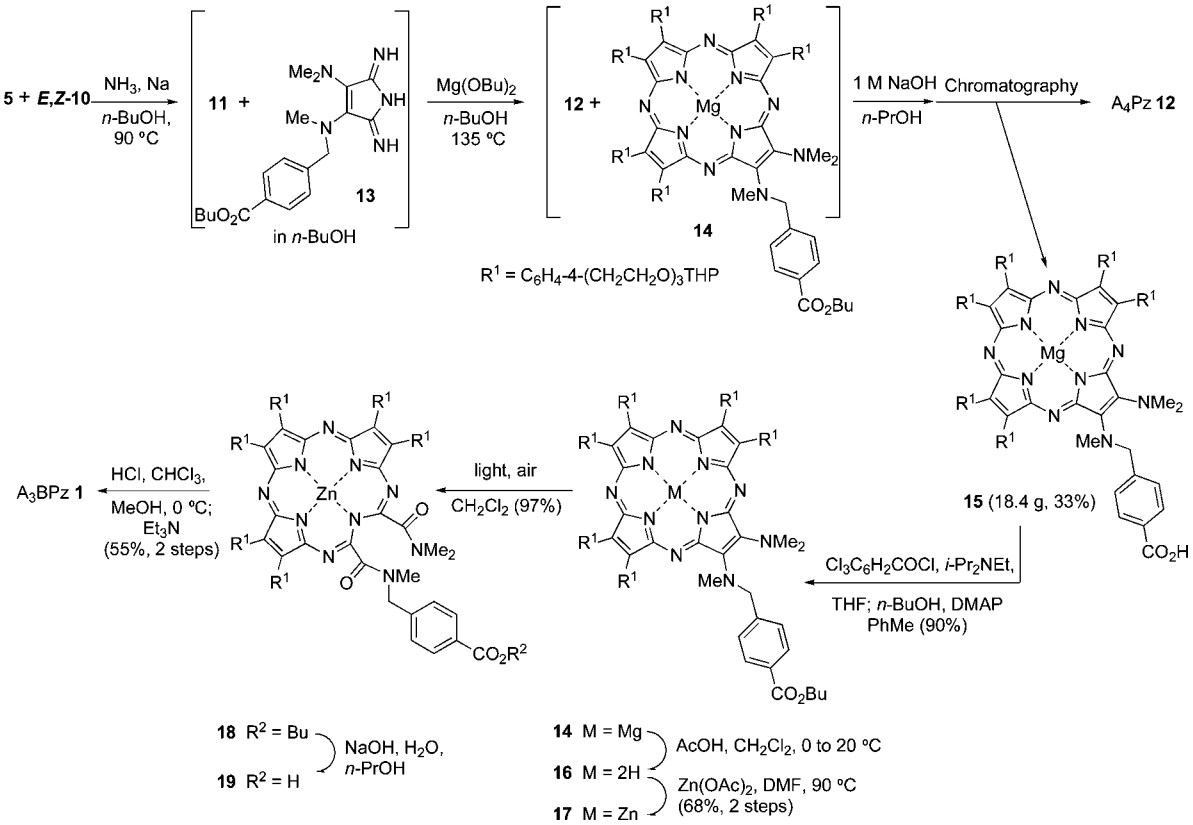

compound, however, is highly polar and although it can be purified by chromatography, its poor stability renders the process difficult and subject to low yields. Instead, a one-pot reaction was developed. The pyrrolidine diimine was generated in situ, and used directly without isolation in the crossed Linstead macrocyclization reaction.[11,17] The crude pyrroline **11** was prepared by reaction of dinitriles ***E*,*Z*-10** with ammonia in anhydrous *n*-butanol, and the resulting solution of **11** was directly added to a freshly prepared solution of magnesium butoxide in *n*-butanol.

Reflux for 16 h gave the desired symmetrical ($A_4$) Pz **12** (31%). This protocol was applied to the synthesis of the unsymmetrical $A_3B$ porphyrazine **14**. Dinitriles ***E*,*Z*-10** and **5** (7:1 ratio) were heated for 16 h in *n*-butanol at 95 °C with a catalytic amount of sodium, under a constant flow of gaseous ammonia (Scheme 4).[16] The mixture of crude pyrrolines **11** and **13** in butanol was immediately added to a preformed solution of magnesium butoxide in *n*-butanol. After 48 h at reflux, the crude mixture of $A_4Pz$ **12** and $A_3BPz$ **14** was saponified to give a mixture of $A_3BPz$ **15**,[18] $A_4Pz$ **12**, and minor impurities. Macrocycle **15** could be purified by chromatography on amberlyst $A_{21}$ or more conveniently silica gel, which afforded the acid **15** in 33% overall yield from dinitrile **5** for the three steps of the synthesis. This process could be successfully applied to 120 g of starting dinitriles ***E*,*Z*-10** and **5**, providing 18.4 g of $A_3BPz$ **15** after three steps and a single chromatographic purification. Such a scale is unusual for unsymmetrical porphyrazines, and these compounds are usually prepared on a small scale (<500 mg) due to low yields and difficulties in purification. To complete the synthesis of the potential PDT photosensitizer **1**, the acid **15** was esterified by *n*-butanol under Yamaguchi conditions,[19] giving ester **14** in

(13) Hudson, R.; Carcenac, M.; Smith, K.; Madden, L.; Clarke, O. J.; Pelegrin, A.; Greenman, J.; Boyle, R. W. *Br. J. Cancer* **2005**, *92*, 1442.
(14) Begland, R. W.; Hartter, D. R.; Jones, F. N.; Sam, D. J.; Sheppard, W. A.; Webster, O. W.; Weigert, F. J. *J. Org. Chem.* **1974**, *39*, 2341.
(15) Irie, M.; Mohri, M. *J. Org. Chem.* **1988**, *53*, 803.
(16) For the use of di-iminopyrrolines in the synthesis of unsymmetrical porphyrazines see: (a) Baumann, T. F.; Barrett, A. G. M.; Hoffman, B. M. *Inorg. Chem.* **1997**, *36*, 5661. (b) Nie, H.; Stern, C. L.; Hoffman, B. M.; Barrett, A. G. M. *Chem. Commun.* **1999**, 703. (c) Nie, H.; Barrett, A. G. M.; Hoffman, B. M. *J. Org. Chem.* **1999**, *64*, 6791. (d) Vasil'ev, S. I.; Kulinich, V. P.; Shaposhnikov, G. P.; Smirnov, R. P. *Russ. J. Gen. Chem.* **1999**, *69*, 314. (e) Bellec, N.; Montalban, A. G.; Williams, D. B. G.; Cook, A. S.; Anderson, M. E.; Feng, X.; Barrett, A. G. M.; Hoffman, B. M. *J. Org. Chem.* **2000**, *65*, 1774. (f) Vasil'ev, S. I.; Kulinich, V. P.; Shaposhnikov, G. P.; Smirnov, R. P. *Russ. J. Gen. Chem.* **2000**, *70*, 304. (g) Montalban, A. G.; Sakellariou, E. G.; Riguet, E.; McCubbin, Q. J.; Barrett, A. G. M.; Hoffman, B. M. *Inorg. Chim. Acta* **2001**, *317*, 143. (h) Kulinich, V. P.; Shaposhnikov, G. P. *Russ. J. Gen. Chem.* **2001**, *71*, 1632. (i) Zhao, M.; Zhong, C.; Stern, C.; Barrett, A. G. M.; Hoffman, B. M. *Inorg. Chem.* **2004**, *43*, 3377. (j) Khelevina, O. G.; Ferro, V. R.; Islyaikin, M. K.; Veselkova, E. A.; Stryapan, M. G.; De la Vega, J. M.; Garcia, J. *Phys. Org. Chem.* **2005**, *18*, 329. (k) Cheng, K. F.; Thai, N. A.; Teague, L. C.; Grohmann, K.; Drain, C. M. *Chem. Commun.* **2005**, 4678. (l) Goslinski, T.; Zhong, C.; Fuchter, M. J.; Stern, C. L.; White, A. J. P.; Barrett, A. G. M.; Hoffman, B. M. *Inorg. Chem.* **2006**, *45*, 3686. (m) Gan, Q.; Xiong, F.; Li, S.; Wang, S.; Shen, S.; Xu, H.; Yang, G. *Inorg. Chem. Commun*. **2005**, *8*, 285. For an example of the use of di-iminoisoindolines in the synthesis of unsymmetrical phthalocyanines see: Kobayashi, N.; Higashi, Y.; Osa, T. *J. Chem. Soc., Chem. Commun.* **1994**, 1785.

(17) It is possible that the macrocyclization reaction involves a sodium template and late transmetalation; see ref 10c.
(18) $A_3BPz$ **15** was obtained in 72% yield when the reaction was performed with chromatographically purified **14**.
(19) (a) Inanaga, J.; Hirata, K.; Katsuki, T.; Yamaguchi, M. A. *Bull. Chem. Soc. Jpn*. **1972**, *52*, 1989. (b) Haslam, E. *Tetrahedron* **1980**, *36*, 2409.

**Scheme 4**




89% yield. Subsequent treatment with acetic acid yielded pure demetalated Pz **16**, which was remetalated with zinc acetate in DMF to give the zinc Pz **17** in 68% global yield. Exposure to air and light at room temperature in $CH_2Cl_2$ gave the *seco*-Pz **18** (97%).[8] Finally, saponification with NaOH in *n*-propanol and acidic deprotection of the THP protecting groups gave the target Pz **1**, which could be purified on lipophilic Sephadex to give **1** (55%).

In conclusion, a large-scale synthesis of a new highly functionalized, water-soluble *seco*-porphyrazine has been achieved. This is a suitable compound for the labeling of biomolecules for imaging and PDT studies. This synthetic procedure has allowed the preparation several grams of the desired Pz **15** in one single reaction sequence in good overall yield.

**Acknowledgment.** We thank the Royal Society and the Wolfson Foundation for a Royal Society Wolfson Research Merit Award (to A.G.M.B.), the Wolfson Foundation for establishing the Wolfson Center for Organic Chemistry in Medical Sciences at Imperial College, the EPSRC for generous support of our research, and Anna M. A. Gonçalves de Oliveira and Sergei Bolshakov (Imperial College London) for assistance with back-up synthesis.

**Supporting Information Available:** Experimental procedures and characterization data for all products and $^1H$ NMR and/or $^{13}C$ NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702481X