Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 45 (2004) 1647–1650

S_NAr reactions of β-substituted porphyrins and the synthesis of meso substituted tetrabenzoporphyrins

Mathias O. Senge* and Ines Bischoff

Institut für Chemie, Universität Potsdam, Karl-Liebknecht-Str. 24-25, D-14476 Golm, Germany

Received 9 November 2003; revised 8 December 2003; accepted 22 December 2003

Abstract—Reaction of 2,3,7,8,12,13,17,18-octaethylporphyrin with LiR reagents containing functional groups readily yields meso substituted derivatives suitable for further transformations with residues such as –*p*-C_6H_5Br, –*p*-C_6H_5–C≡CH, –*p*-C_6H_5–NH_2 or –$(CH_2)_3$–CH=CH_2. Similar reactions of tetrabenzoporphyrin with alkyllithium reagents afforded the first entry into meso mono- and dialkylsubstituted tetrabenzoporphyrins while reaction of bicyclo[2.2.2]oct-type masked isoindole precursors with LiR followed by in situ retro-Diels–Alder reaction also afforded the 5-phenyl and 5,10-diphenyltetrabenzoporphyrins in high purity.

The introduction of functional groups into easily available, pre-made tetrapyrroles remains one of the pressing targets in porphyrin chemistry to further advance applications in biology, medicine, and materials science.[1] One such method utilizes the regioselective nucleophilic substitution of porphyrins in the meso position with organolithium reagents.[2] It allows a facile introduction of functional groups into simple 5,15-disubstituted porphyrins and can be used to substitute all four meso positions in β-substituted porphyrins in sequence.[3] In order to develop further the synthetic utility of this method we have now targeted octaethylporphyrin **1** and tetrabenzoporphyrin **8** as exemplars for this reaction.

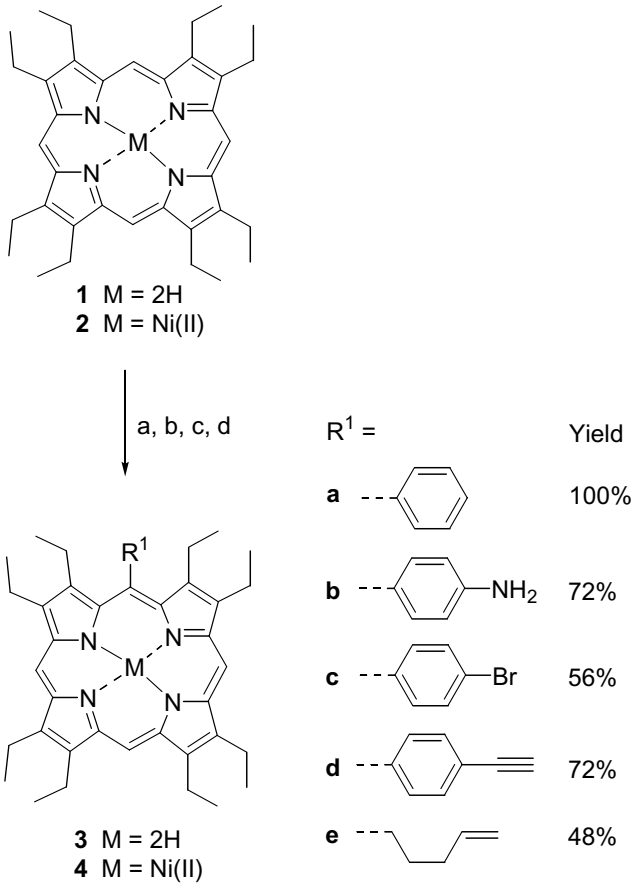
Due to its excellent solubility and diverse reactivity octaethylporphyrin **1** is one of the most widely used frameworks for complex porphyrinic systems and serves as a standard test case for new reactions.[4] Improved access to derivatives of **1** amenable to subsequent C–C coupling reactions would impact many areas of applied research. In contrast, although tetrabenzoporphyrin derivatives have significant potential in optics, tumor therapy and materials science, their characterization and the advancement of applications is hampered by their low solubility and undeveloped chemistry.[5]

First, we reacted octaethylporphyrin **1** with a variety of organolithium reagents bearing functional groups suitable for later C–C coupling reactions (e.g., aryl-Br for Heck-type reactions, aryl-C≡CH for Glaser couplings, alkyl-CH=CH_2 for metathesis or ozonolysis, –NH_2 for amide formation) (Scheme 1). As expected simple reagents such as Li^{n}Bu or LiPh[3] led to the target porphyrins in good yields (e.g., **3b** 72%,[6] **3c** 56%, **3d** 72%, and **3e** 48%). Sterically hindered reagents such as Li^{t}Bu or Li^{i}Pr did not react with **1** and thus an excess of Li^{t}Bu can be used for easier in situ preparation of reactive organolithium reagents preventing any formation of butylated by-products. Analogous transformations of the nickel(II) complex **2** resulted in differences in reactivity and yields to those observed for reactions with Li^{n}Bu or LiPh (for example, lower yields for arylations: **4b** 59%, **4c** 40%; higher for alkylations: **4e** 60%).

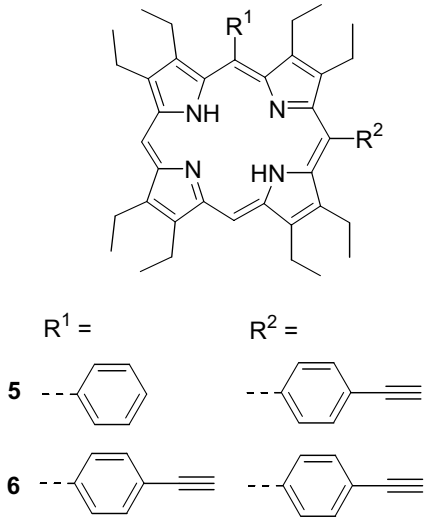
In line with our prediction from mechanistic studies,[2b] meso aryl substituents direct subsequent substitutions to the neighboring meso position. Thus, **3a** was transformed in 61% yield to the 5,10 derivative **5** while **6** was obtained in 65% from **3d**. Reactions of **1** with more complex LiR reagents can be performed with ease in a manner similar to those of β-unsubstituted porphyrins.[3a]

Keywords: Nucleophilic aromatic substitution; Tetrabenzoporphyrins; C–C coupling reactions; Organolithium reagents; Tetrapyrroles.
* Corresponding author. Tel.: +49-331-977-5187; fax: +49-331-977-5059; e-mail: mosenge@chem.uni-potsdam.de

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.12.121



Scheme 1. Synthesis of meso substituted 2,3,7,8,12,13,17,18-octaethylporphyrins. (a) LiR[1], THF, −40 to −80 °C; (b) 1 h, rt; (c) H_2O, 15 min; (d) DDQ, 1 h.



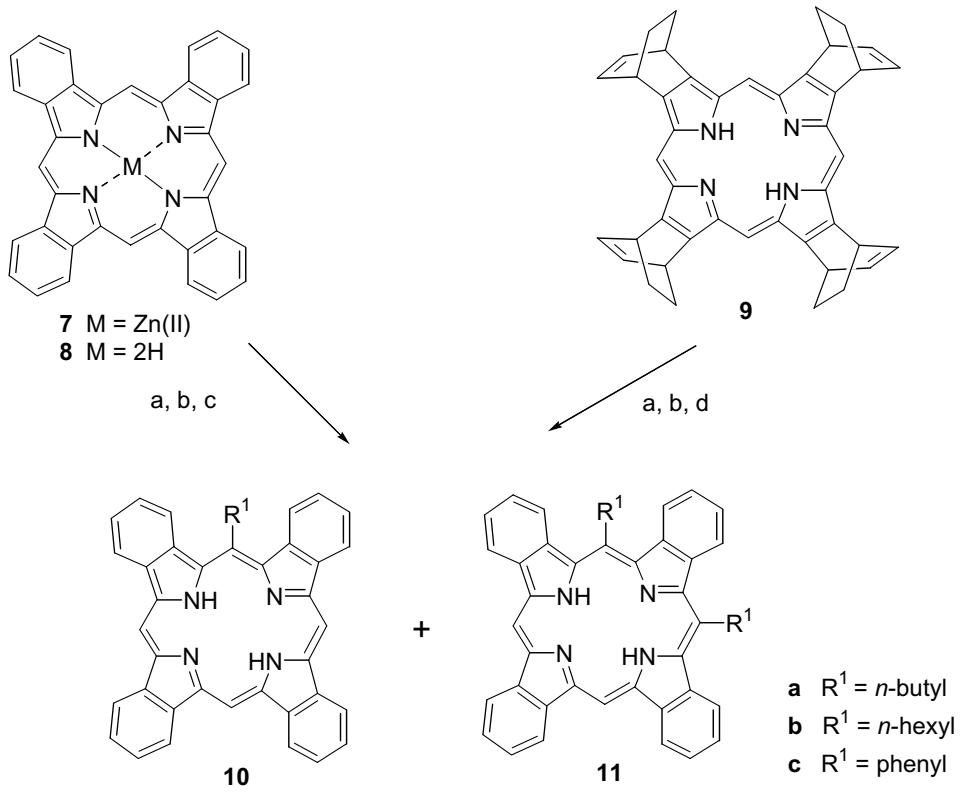
Encouraged by these results we anticipated that the introduction of solubility-enhancing groups into the meso position of tetrabenzoporphyrin **8** by way of similar reactions should be possible. So far, synthetic attempts to improve access to benzoporphyrins have been aimed at methods for the modification of all four meso positions with one type of residue[7] or focused on the modification of the annulated rings.[5,8] A significant breakthrough has been Ono's method to first prepare soluble benzoporphyrin precursors with masked isoindole units followed by a retro-Diels–Alder reaction.[9] However, as yet this method allows no simple variation of the meso substituents. It remains a significant problem to obtain very pure samples of individual tetrabenzoporphyrins with 1–4 meso-aryl residues and this hampers further progress in understanding the influence of individual substituents on the optical and physicochemical properties.[5,10] So far, compounds such as **10c** or **11c** could only be prepared from mixed condensation reactions with tedious chromatographic work-up. Similarly, meso alkyltetrabenzoporphyrins have remained elusive.[10b]

In order to investigate the S_NAr reactions of this porphyrin system we reacted (tetrabenzoporphyrinato)zinc(II) **7**[11] with Li^{n}Bu under conditions similar to those used for **1** (Scheme 2). Three demetalated products were obtained after work-up and identified as the free base **8** of the starting material (10%), the monoalkylated product **10a** (43%), and the 5,10-dibutylated porphyrin **11a** (13%). A similar reaction with Li *n*-C_6H_{13} gave **8** (32%), **10b** (38%), and **11b** (9%).[12] Attempts to increase the yield of the dialkylation product by using 8 equiv of Li *n*-C_6H_{13} or higher temperatures gave **8**, **10b**, and **11b** in 46%, 14%, and 6% yield, respectively. No reaction took place with either LiPh, Li^{t}Bu or Li *n*-C_6H_4–NLi_2.

The two meso substituted porphyrins **10** and **11** could be separated from each other by column chromatography and were obtained in high purity allowing full spectroscopic characterizations. Nevertheless, the meso monosubstituted derivatives were still very insoluble and thus spectroscopic analyses were performed on the respective dications. Both **11a** and **11b** are soluble in organic solvents such as CH_2Cl_2 or acetic acid ethyl ester. Based on the observed dialkylation taking place tetrabenzoporphyrin shows a reactivity toward LiR similar to that of unsubstituted porphyrin.[13]

Next, we planned to monosubstitute the more soluble tetrabenzoporphyrin precursor **9** (as the diastereomeric mixture) developed by Ono and co-workers,[9] expecting a reactivity similar to **1**. However, reaction of **9** with Li^{n}Bu gave the monosubstituted derivative as the main product accompanied by smaller amounts of the disubstituted compound. The two compounds could not be separated at this stage. Thus, we performed the substitution and subsequent retro-Diels–Alder reaction as a one-pot reaction and obtained **10a** and **11a** in 43% and 7% yield, respectively. Chromatographic work-up of this reaction was fairly simple. However, this was counterbalanced by the lengthy synthesis of the isoindole porphyrin precursor.[9] In contrast to **7**, porphyrin **9** reacted easily with LiPh to yield **10c** (52%) and **11c** (8%). This reaction gave both compounds in high purity and for the first time allowed detailed spectroscopic investigations on such systems.[14]

Although the reaction of tetrabenzoporphyrins with LiR requires further study it appears to offer a relatively



Scheme 2. Synthesis of meso substituted tetrabenzoporphyrins. (a) LiR^1, THF, −30 to −80 °C; (b) H_2O, 10 min; (c) DDQ, 1 h; (d) DDQ, 200 °C, 1 h.

simple entry into meso substituted tetrabenzoporphyrin derivatives and has shown its potential by giving access to the first meso alkylated tetrabenzoporphyrins. Preparation of the 5,10 derivative **11** via an S_NAr reaction with **10** in better yields and subsequent conversion to the meso tri- and tetrasubstituted derivatives including those with mixed substituent pattern should be straightforward as the solubility increases with each additional meso substituent.

Acknowledgements

This work was supported by grants from the Deutsche Forschungsgemeinschaft (Se543/5-2).

References and notes

1. *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic: San Diego, 2000; Vol. 1.
2. (a) Senge, M. O.; Kalisch, W. W.; Bischoff, I. *Chem. Eur. J.* **2000**, *6*, 2721–2738; (b) Feng, X.; Bischoff, I.; Senge, M. O. *J. Org. Chem.* **2001**, *66*, 8693–8700.
3. (a) Feng, X.; Senge, M. O. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1030–1038; (b) Senge, M. O.; Bischoff, I. *Eur. J. Org. Chem.* **2001**, 1735–1751.
4. Vicente, M. G. H. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic: San Diego, 2000; Vol. 1, pp 149–199.
5. Lash, T. D. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic: San Diego, 2000; Vol. 2, pp 125–199.
6. Typical procedure for **3b**: For preparation of the organolithium reagent *p*-bromoaniline (1 g, 5 mmol) was dissolved in 15 mL diethyl ether in a 250 mL Schlenk tube. Within 1 h, 6 mL Li^{n}Bu (2.5 M in *n*-hexane, 15 mmol) or Li^{t}Bu were added dropwise at 0 °C (Ar) to the reaction mixture. The cold bath was removed and the yellow mixture stirred for 1 h at room temperature. Porphyrin **1** (100 mg, 0.19 mmol) was dissolved in 60 mL THF and cooled to −40 °C. The cold solution of the porphyrin was added under Ar to the organolithium reagent and stirred for 1 h at room temperature. The cold bath was removed and the mixture stirred for 60 min, followed by addition of 5 mL water in 5 mL THF. After stirring for an additional 30 min, 10–15 equiv of DDQ (ca. 0.06 M as a solution in THF) were added. After 60 min the reaction mixture was filtered through neutral alumina, washed with dichloromethane, and concentrated in vacuo. Column chromatography on neutral alumina (Brockmann grade III) eluting with *n*-hexane/dichloromethane (6:1, v/v) yielded the target compound **3b** as the most polar fraction and gave 85 mg (0.14 mmol, 72%) of purple crystals after recrystallization from dichloromethane/methanol. Mp 259 °C; $R_f = 0.24$ (*n*-hexane/dichloromethane, 4:1 v/v, alumina, 6×3 cm); ^{1}H NMR (500 MHz, $CDCl_3$, TMS): $\delta = -3.05$, 2.99 (each s, 2H, N*H*), 1.19 (t, 6H, $^3J = 7.3$ Hz, 2×CH_2CH_3), 1.89 (t, 6H, $^3J = 7.4$ Hz, 2×CH_2CH_3), 1.95 (t, 12H, $^3J = 7.5$ Hz, 4×CH_2CH_3), 2.94 (q, 4H, $^3J = 7.4$ Hz, 2×CH_2CH_3), 3.95 (s, 2H, phenyl–NH_2), 4.08 (m, 12H, 6×CH_2CH_3), 6.96 (d, 2H, $^3J = 3.8$ Hz, H_{Ph}), 7.95 (d, 2H, $^3J = 3.8$ Hz, H_{Ph}), 9.95 (s, 1H, 15-H), 10.19 ppm (s, 2H, 10,20-H); MS (EI, 80 eV), *m*/*z* (%): 625 (100) [M^+], 610 (6) [M^+-CH_3], 596 (4) [$M^+-C_2H_5$],

313 (11) [M^{2+}]; UV–vis (CH_2Cl_2+1% NEt_3): $\lambda_{max}(\log\varepsilon) = 406$ (5.45), 505 (4.39), 537 (4.07), 573 (3.99), 625 nm (3.49); HRMS [$C_{42}H_{51}N_4$]: calcd 625.4144, found 625.4172.

7. (a) Vinogradov, S. A.; Wilson, D. F. *Tetrahedron Lett.* **1998**, *39*, 8935–8938; (b) Finikova, O.; Glakin, A.; Rozhkov, V.; Cordero, M.; Hägerhäll, C.; Vinogradov, S. A. *J. Am. Chem. Soc.* **2003**, *125*, 4882–4893.
8. Vicente, M. G. H.; Jaquinod, L.; Khoury, R. G.; Madrona, A. Y.; Smith, K. M. *Tetrahedron Lett.* **1999**, *40*, 8763–8766.
9. Ito, S.; Murashima, T.; Uno, H.; Ono, N. *Chem. Commun.* **1998**, 1661–1662.
10. (a) Ichimura, K.; Sakuragi, M.; Morii, H.; Yasuike, M.; Fukui, M.; Ohno, O. *Inorg. Chim. Acta* **1990**, *176*, 31–33; (b) Ichimura, K.; Sakuragi, M.; Morii, H.; Yasuike, M.; Toba, Y.; Fukui, M. *Inorg. Chim. Acta* **1991**, *186*, 95–101; (c) Ichimura, K.; Sakuragi, M.; Morii, H.; Yasuike, M.; Fukui, M.; Ohno, O. *Inorg. Chim. Acta* **1991**, *182*, 83–86.
11. Vogler, A.; Kunkely, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 760.
12. *Reaction of (tetrabenzoporphyrinato)zinc(II) with n-hexyl lithium*: Benzoporphyrin **7** (100 mg, 0.17 mmol) was suspended in 150 mL THF and cooled to −30 °C. After addition of 0.6 mL *n*-hexyllithium (1.5 M, 0.9 mmol) the green-blue reaction mixture turned first purple then brown. After stirring for 30 min, water (1 mL) was added, no change of color was observed. The cold bath was removed and 9 mL of a 0.6 M solution of DDQ was added after 10 min, resulting in a color change to green. Polar impurities were removed via chromatography on silica with THF/pyridine (9:1, v/v). TLC showed three green product fractions. A first silica gel column (*n*-hexane/acetic acid ethyl ester (99:1, v/v) resulted in isolation of 10 mg blue of crystals of the dihexylated benzoporphyrin **11b** after recrystallization from dichloromethane/*n*-hexane (0.24 mmol, 9%). Purification of the second and third fraction was achieved with another silica gel column (THF/pyridine, 99:1, v/v). The second TLC fraction consisted of 38 mg (0.06 mmol, 38%) **10b** while the third fraction was identified as demetalated benzoporphyrin **8** (27 mg, 0.05 mmol, 32%). *5-Hexyl-tetrabenzoporphyrin* **10b**: Mp > 300 °C; ^{1}H NMR (500 MHz, $CDCl_3$+10% CF_3COOD, $SiMe_4$): $\delta = 1.07$ (m, 3H, $(CH_2)_5CH_3$), 1.58 (m, 2H, $(CH_2)_4CH_2CH_3$), 1.74 (m, 2H, $(CH_2)_3CH_2CH_2CH_3$), 2.19 (m, 2H, $CH_2CH_2CH_2(CH_2)_3$), 2.87 (m, 2H, $CH_2CH_2(CH_2)_4$), 5.49 (m, 2H, $CH_2(CH_2)_5$), 8.35, 8.49 (each m, 8H, 2^1,2^4,7^1,7^4,12^1,12^4,17^1,17^4-H_{benzo}), 9.33, 9.46, 9.52 (each m, 2H, 2H, 4H, 2^2,2^3,7^2,7^3, 12^2,12^3,17^2,17^3-H_{benzo}), 10.84 (s, 1H, 15-H), 11.02 ppm (s, 2H, 10,20-H); MS (EI, 80 eV), *m*/*z* (%): 594 (100) [M^+], 523 (37) [$M^+-C_5H_{11}$], 297 (7) [M^{2+}]; UV–vis (CH_2Cl_2): $\lambda_{max}(\log\varepsilon) = 397$ (4.13), 422 (4.78), 435 (4.82), 571 (3.50), 605 (4.10), 609 (4.09), 664 nm (3.76); HRMS [$C_{42}H_{34}N_4$]: calcd 594.2783, found 594.2758. *5,10-Dihexyl-tetrabenzoporphyrin* **11b**: Mp > 300 °C; ^{1}H NMR (500 MHz, $CDCl_3$, $SiMe_4$): $\delta = -1.39$ (s, 2H, N*H*), 0.86 (m, 6H, $2\times(CH_2)_5CH_3$), 1.33 (m, 4H, $2\times(CH_2)_4CH_2$ CH_3), 1.40 (m, 4H, $2\times(CH_2)_3CH_2CH_2CH_3$), 1.80 (m, 4H, $CH_2CH_2CH_2(CH_2)_3$), 2.29 (m, 4H, $CH_2CH_2(CH_2)_4$), 5.31 (m, 4H, $CH_2(CH_2)_5$), 7.72, 8.00, 8.10 (each m, 4H, 2H, 2H, 2^1,2^4,7^1,7^4,12^1,12^4,17^1,17^4-H_{benzo}), 9.00, 9.20, 9.43 (each m, 2H, 4H, 2H, 2^2,2^3,7^2,7^3,12^2,12^3,17^2,17^3-H_{benzo}), 10.17 ppm (s, 2H, 15,20-H); MS (EI, 80 eV), *m*/*z* (%): 679 (84) [M^++H], 678 (59) [M^+], 607 (26) [$M^+-C_5H_{11}$]; UV–vis (CH_2Cl_2): $\lambda_{max}(\log\varepsilon) = 397$ (4.57), 422 (5.14), 435 (5.12), 528 (3.46), 568 (3.98), 608 (4.57), 665 nm (4.34); HRMS [$C_{48}H_{46}N_4$] calcd 678.3743, found 678.3722.
13. Hatscher, S.; Senge, M. O. *Tetrahedron Lett.* **2003**, *44*, 157–160.
14. The porphyrin solution was cooled to 0 °C and treated with LiPh in THF. After 15 min the mixture was warmed to 30 °C and stirred for another 15 min. After cooling to 0 °C, 1 mL water was added, resulting in a color change to green. The mixture was stirred for 18 h under air to complete the oxidation and turned brown. The reaction flask was purged with Ar and heated under vacuum for 1 h at 200 °C. TLC showed two green bands and a weak, brown residue at the baseline. Chromatography on neutral alumina (Brockmann grade III, CH_2Cl_2/*n*-hexane, 2:1, v/v) yielded first **11c**[15] followed by **10c**.
15. Analytical data for 5-phenyl-tetrabenzoporphyrin **10c**: Mp > 300 °C; ^{1}H NMR (500 MHz, $CDCl_3$+10% CF_3COOD, $SiMe_4$): $\delta = 7.57$ (d, 2H, $^3J = 4.1$ Hz, H_{Ph}), 7.86 (t, 2H, $^3J = 7.4$ Hz, H_{Ph}), 8.03 (m, 2H, 2^3,2^4,7^1,7^2,12^3, 12^4,17^1,17^2-H_{benzo}), 8.12 (t, 1H, $^3J = 7.6$ Hz, H_{Ph}), 8.20, 8.39 (each m, 2H, 2H, 2^3,2^4,7^1,7^2,12^3,12^4,17^1,17^2-H_{benzo}), 8.49 (m, 4H, 2^2,7^3,12^2,17^3-H_{benzo}), 9.38 (m, 2H, 2^3,2^4,7^1,7^2, 12^3,12^4,17^1,17^2-H_{benzo}), 9.62 (m, 4H, 2^1,7^4,12^1,17^4-H_{benzo}), 10.97 (s, 1H, 15-H), 11.09 ppm (s, 2H, 10,20-H); MS (EI, 80 eV), *m*/*z* (%): 586 (100) [M^+], 293 (14) [M^{2+}]; UV–vis (CH_2Cl_2): $\lambda_{max}(\log\varepsilon) = 389$ (4.11), 420 (4.75), 433 (4.68), 558 (3.39), 599 (3.96), 608 (4.02), 664 nm (3.79); HRMS [$C_{42}H_{26}N_4$]: calcd 586.2157, found 586.2159.