Pergamon

Tetrahedron 56 (2000) 7661–7666

TETRAHEDRON

Synthesis of Benzochlorins and Rhodinobenzochlorins

Avinash S. Phadke,[a,*] Byron C. Robinson,[a,†] Kathleen M. Barkigia[b,‡] and Jack Fajer[b,§]

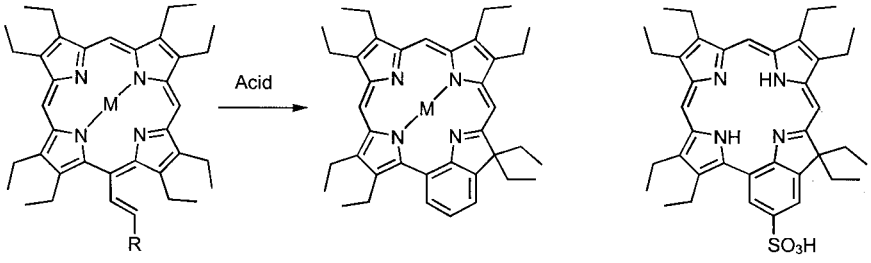
[a]*Miravant Pharmaceuticals, 336 Bollay Drive, Santa Barbara, CA 93117, USA*
[b]*Department of Applied Science, Brookhaven National Laboratory, Upton, NY 11973, USA*

Received 25 April 2000; revised 3 August 2000

Abstract—The mechanism of the cyclization of *meso*-(1-hydroxy-2-propenyl)octaethylporphyrin to octaethylbenzochlorin is proposed. Chlorin intermediates were isolated, characterized and then converted to octaethylbenzochlorin. A rhodinobenzochlorin was isolated on demetallation of Ni coprobenzochlorin with methane sulfonic acid and its structure was confirmed by X-ray crystallography.

Benzochlorins and their derivatives are promising drug candidates in the field of photodynamic therapy.[1] Arnold et al. was first to report the synthesis of Ni-octaethylbenzochlorin (NiOEBC) (**5**)[2] (Scheme 1) from Ni *meso*-vinylformyloctaethylporphyrin (**1**), although the exact mechanism of cyclization is still not clear. Demetallation of NiOEBC (**5**) is difficult, and when H_2SO_4 is used, a mixture of octaethylbenzochlorin (OEBC) (**7**) as well as the sulfonated octaethylbenzochlorin (OEBCS) (**8**) is obtained.[3] Smith et al.[4] used Cu *meso*-vinylformyloctaethylporphyrin (**2**) to synthesize Cu octaethylbenzochlorin (CuOEBC) (**6**), which was reportedly easier to demetallate than NiOEBC. Improvements to the formation of OEBC include the cyclization of *meso*-(1-hydroxy-2-propenyl)-octaethylporphyrin (**3**) in concentrated sulfuric acid to give OEBC (**7**).[3] In this reported procedure the reaction time is five minutes, and longer reaction times leads to the formation of the OEBCS (**8**) (Scheme 1).

In our laboratory, we have investigated the synthesis of OEBC from *meso*-(1-hydroxy-2-propenyl)octaethylporphyrin (**3**) in detail, and have modified the reaction conditions to yield exclusively OEBC on 100 g scale.[5] Investigation into the acid catalyzed cyclization of (**3**) to (**7**) leads to some interesting observations into the mechanism of cyclization. Treatment of (**3**) with phosphoric acid at 80°C leads to the rapid formation of three compounds by TLC: (i) OEBC and (ii) two more polar compounds



1. R = CHO, M = Ni
2 R = CHO, M = Cu
3 R = CH_2OH, M = 2H
4. R = $CH_2NMe_3^+I^-$, M = Ni

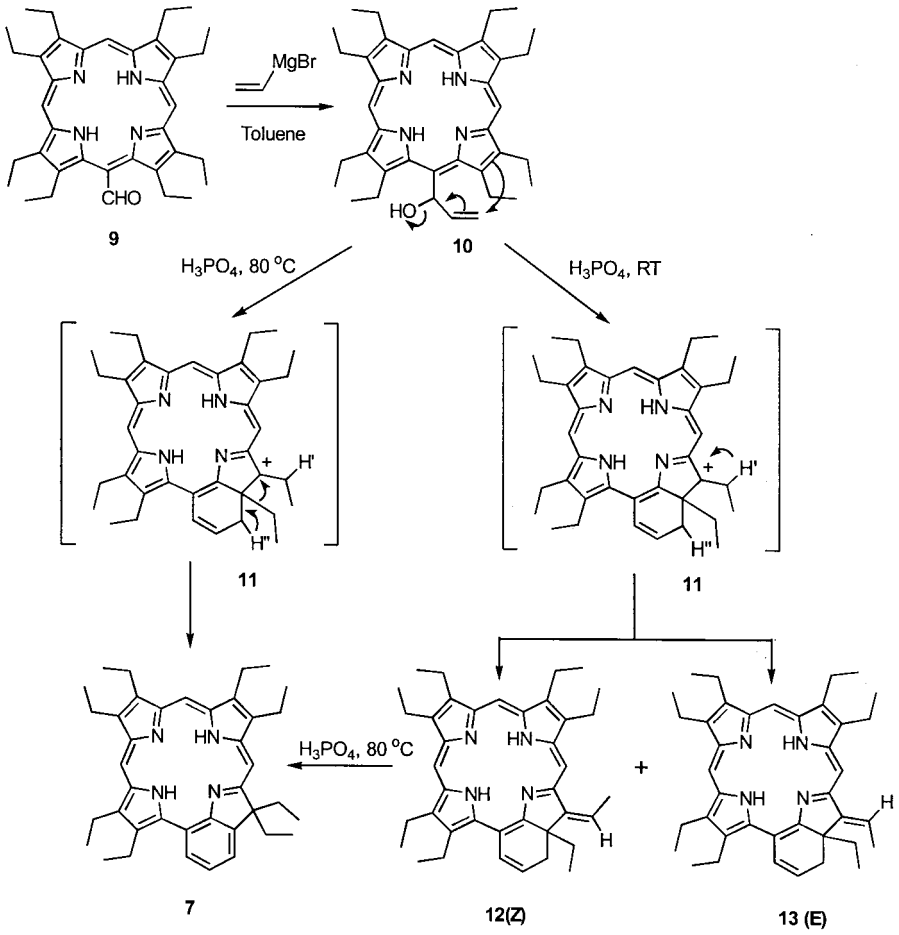
5 M = Ni
6. M = Cu
7. M = 2H

8

Scheme 1.

Keywords: chlorins and derivatives; photodynamic therapy.
* Corresponding author. Tel.: +1-805-685-9880; fax: +1-805-685-7981; e-mail: aphadke@miravant.com
† E-mail: brobinso@miravant.com.
‡ E-mail: barkigia@ckb.chm.bnl.gov
§ E-mail: fajerj@bnl.gov.

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00692-X



Scheme 2.

absorbing at 683 nm. Prolonged heating at 80°C converted the polar compounds to OEBC. An identical pattern was observed when the hydroxy porphyrin (**10**) was treated with phosphoric acid (Scheme 2). The hydroxy porphyrin (**10**) (prepared by reacting *meso*-formyl octaethylporphyrin (**9**) with vinyl magnesium bromide in toluene) was treated with phosphoric acid and stirred overnight at room temperature. A TLC of the reaction mixture showed three compounds, the least polar compound being OEBC. The remaining two polar compounds, which were very close in R_f, had a band I absorption at 683 nm.

The polar compounds were isolated by preparative TLC and identified by NMR and MS analysis. NMR identified the two compounds as (**12**) and (**13**), the *Z* and *E* isomers of the exocyclic double bond. It is clear from these observations that two pathways to the formation of OEBC are possible from (**3**) or (**10**), which involve the initial formation of (**11**) (Scheme 2). As shown in Scheme 2, compounds (**12**) and (**13**) are formed by the loss of H′ in intermediate (**11**). When compounds (**12**) and (**13**) were heated in phosphoric acid at 80°C, the allylic proton of the six membered ring is lost with concomitant migration of the ethyl group to give OEBC (**7**). Alternatively, OEBC may be formed from (**11**) via the loss of H″ followed by concomitant migration of the ethyl group.

A ^{1}H NMR analysis of compounds (**12**) and (**13**) shows some interesting features. In compound (**12**) the methyl group (d, δ 2.74 ppm) on the exocyclic double bond is in close proximity to the *meso*-hydrogen adjacent to the reduced pyrrole ring. As a result this methyl group lies in a deshielding region of the macrocyclic ring current. The same methyl group in (**13**) resonates at δ 2.47 ppm. Similarly, the olefinic hydrogen on the exocyclic double bond in compound (**13**) (q, δ 7.34 ppm) is deshielded compared to the olefinic proton in compound (**12**) (q, δ 6.22 ppm). Also, in compound **12** the CH_3 of the ethyl group on the sp^3 C of the reduced pyrrole ring resonates at δ 0.3 ppm because it is above the plane of the macrocyle and is shielded by the ring current. Whereas, the same CH_3 in compound **13** resonates at δ 0.03 ppm. This difference is probably due the proximity of the olefinic CH_3 group in **12** pushing the ethyl group above the plane of the ring compared to the same ethyl in compound **13**. Portions of both ^{1}H NMR's are shown in Fig. 1 (**12**) and Fig. 2 (**13**). The ^{1}H NMR assignments were in agreement with similar compounds reported in literature.[6,7] The Nickel derivatives of compounds (**12**) and (**13**), which were synthesized by thermolysis of (**4**) in 1,2-dichloroethane, were named Australochlorins by Arnold et al.[6]

Synthesis of a rhodinobenzochlorin

In an attempt to synthesize functionalized benzochlorins,

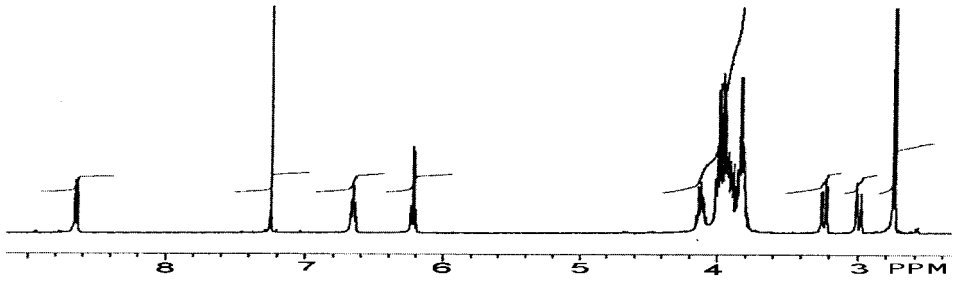


Figure 1. (**12**).

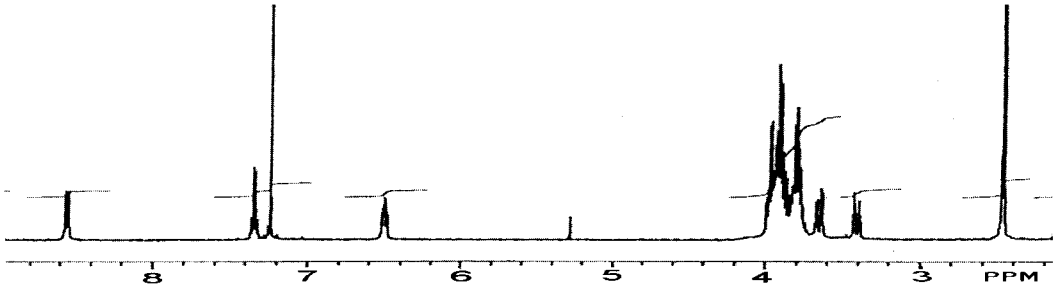
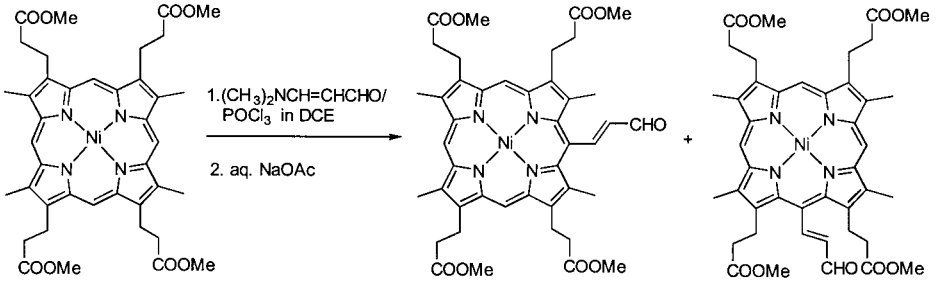
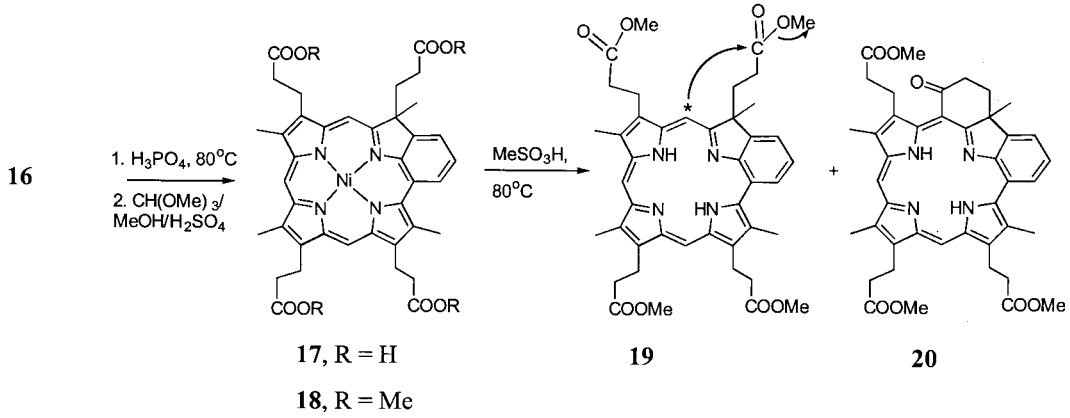


Figure 2. (**13**).



14 **15** **16**

Scheme 3.



Scheme 4.

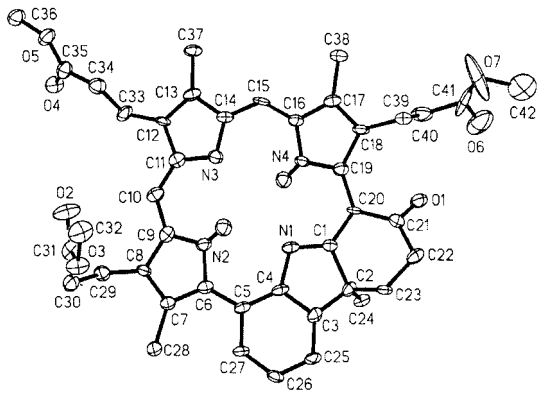


Figure 3.

Ni-coproporphyrin II tetramethyl ester (**14**) was reacted with dimethylaminoacrolein and phosphorous oxychloride as reported in the literature.[4] The reaction product was a isomeric mixture of the *meso*-vinylformyl porphyrins (**15**) and (**16**) (Scheme 3). These two isomers were separated by column chromatography on silica gel. Isomer (**16**) was used for further reactions.

Ni *meso*-vinylformylporphyrins have been cyclized using concentrated H_2SO_4,[3,4] but we chose to use phosphoric acid at 80°C (4 h) to avoid possible sulfonation of product **17** (Scheme 4). The product obtained was the Ni-benzochlorin tetracarboxylic acid (**17**) which was then esterified using trimethylorthoformate/methanol/H_2SO_4[8] to afford the Ni-benzochlorin (**18**). Choosing not to use H_2SO_4 for demetallation of (**18**) due to the possibility of sulfonating the exocyclic ring, we successfully demetallated (**18**) using methanesulfonic acid at 80°C (4 h) to reveal two compounds by TLC.

These were separated using silica gel chromatography using 1–2.5% acetone/CH_2Cl_2 as the elution solvent. The least polar compound had a band I absorption at 657 nm, and was characterized by ^{1}H NMR to be benzochlorin (**19**). The second, more polar compound, had a band I absorption at 700 nm, and was characterized by ^{1}H NMR to be (**20**). In compound (**19**), the *meso*-carbon adjacent to the reduced pyrrole ring resonates at δ 8.01 ppm. The remaining *meso*-hydrogens resonate at δ 8.56 and δ 9.24 ppm. In (**20**) only two *meso*-hydrogen resonances are seen at δ 8.47 and δ 8.92 ppm. This indicated that one of the propionate side chains adjacent to the *meso* position had cyclized onto the *meso*-carbon. The hydrogens on the propionate chain ($CH_2CH_2CO_2Me$) attached to the sp^3 ring carbon on the reduced pyrrole in (**19**) resonate at δ 1.15 and δ 1.2 ppm. In (**20**) these are not observed. An X-ray crystallographic determination provided an unambiguous identification of compound (**20**) and the first stereochemical parameters for this new class of benzochlorin.[9] The ORTEP diagram and UV–Vis spectrum of (**20**) are shown in Figs. 3 and 4, respectively.

Experimental

All the reactions were performed under subdued lighting. Organic extracts were dried over anhydrous Na_2SO_4. Solvents and reagents were purchased from commercial sources and used without further purification unless otherwise mentioned. Silica gel 60 (230–400 mesh) was used for column chromatography. Analytical thin layer chromatography was performed on Merck 60 F254 silica gel (precoated on aluminum). Preparative TLC was performed on Alltech Uniplate silica gel G (20×20 cm, 250 μ). ^{1}H spectra were recorded using a Unity Inova Varian 500 MHz spectrometer, chemical shifts of proton spectra are expressed in parts per million relative to the chloroform signal in deuterated chloroform (set at 7.24 ppm). Electronic spectra were recorded on a Beckman DU 640 spectrophotometer and Cary Bio100. High-resolution mass spectra were obtained on a VG 70SE double focussing mass spectrometer equipped with an oversize data system at the University of California Santa Barbara by Dr. James Pavlovich.

Compounds (12) and (13)

To a solution of (**9**) (100 mg) in hot (60°C) toluene (10 ml) was added excess Vinyl magnesiumbromide (2 ml, 1 M in THF). The reaction was stirred at room temperature for 2 h. The reaction was diluted with 10% aq. NH_4Cl (10 ml) and

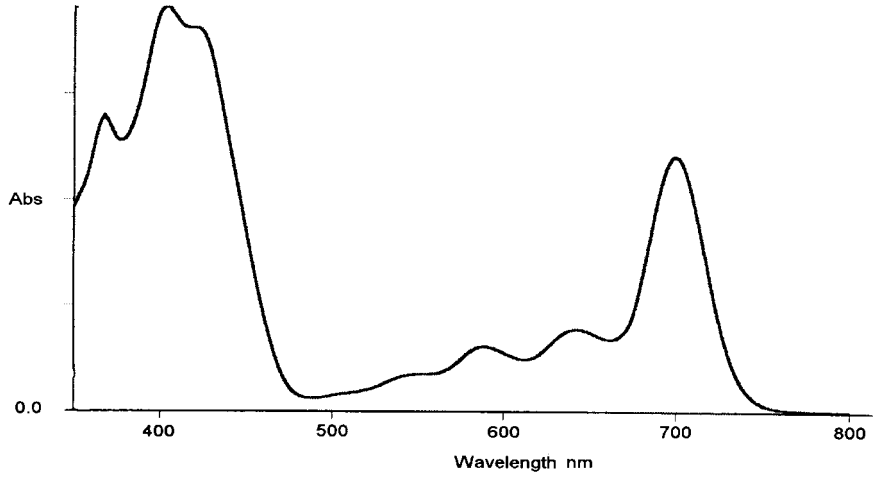


Figure 4.

extracted with CH_2Cl_2 (2×10 ml), dried and evaporated to dryness. The residue was dissolved in H_3PO_4 (2 ml) and stirred at room temperature overnight. The reaction was diluted with 5% aq. $NaHCO_3$, and extracted with CH_2Cl_2 (3×50 ml). The organic layer was washed with water (1×50 ml), dried, and evaporated to dryness. The product was a mixture of three compounds. These were isolated using preparative TLC (solvent 40% hexane/CH_2Cl_2]. The least polar band isolated was OEBC (40 mg,). The first green band isolated was compound (**12**) (8 mg,), and the following green band was compound (**13**) (8 mg).

(12). UV–Vis (CH_2Cl_2) λ max (ε): 425 (124000), 523 (9800), 561 (7000), 683 (19000) nm. ^{1}H NMR ($CDCl_3$); δ −2.08, −1.55 (2s, 2H, N*H*), 0.30 (t, 3H, CH_3CH$_2$ on the sp^3 carbon of the reduced pyrrole), 1.4, 1.55 (2m, 2H, CH$_3$CH_2 on the sp^3 carbon of the reduced pyrrole), 1.8 (m, 15H, CH_3CH$_2$), 1.95 (m, 3H, CH_3CH$_2$). 2.74 (d, 3H, =CHCH_3), 3.0 (d, 1H, exocyclic ring CH=CH–CH_2), 3.25 (dd, 1H, exocyclic ring CH=CH–CH_2), 3.8 (m, 4H, CH_2CH$_3$), 3.95 (m, 6H, CH_2CH$_3$), 4.14 (m, 2H, CH$_3$CH_2), 6.22 (q, 1H, =C*H*CH$_3$), 6.65 (m, 1H, exocyclic ring CH=C*H*–CH$_2$), 8.65 (dd, 1H, exocyclic ring C*H*=CH–CH$_2$), 9.41, 9.57, 9.66 (3s, 3H, *meso*-H). HRMS: calcd: 572.3878, found: 572.3860.

(13). UV–Vis (CH_2Cl_2): 425, 519, 559, 683 nm. ^{1}H NMR ($CDCl_3$): δ −1.9, −1.45 (2s, 2H, N*H*), 0.03 (t, 3H, CH_3CH$_2$ on the sp^3 carbon of the reduced pyrrole), 1.8 (m, 18H, CH_3CH$_2$), 1.95, 2.1 (2m, 2H, CH$_3$CH_2 on the sp^3 carbon of the reduced pyrrole), 2.47 (d, 3H, =CHCH_3), 3.4 (d, 1H, exocyclic ring CH=CH–CH_2), 3.65 (dd, 1H, exocyclic ring CH=CH–CH_2), 3.8 (m, 4H, CH_2CH$_3$), 3.92 (m, 8H, CH_2CH$_3$), 6.5 (m, 1H, exocyclic ring CH=C*H*–CH$_2$), 7.34 (q, 1H, =C*H*CH$_3$), 8.55 (dd, 1H, exocyclic ring C*H*=CH–CH$_2$), 9.21, 9.48, 9.63 (3s, 3H, *meso*-H). HRMS: calcd: 572.3878; found: 572.3871.

Compounds (15) and (16)

Dimethylaminoacrolein (2 ml) was dissolved in dichloroethane (25 ml) and cooled in a dry ice/acetone bath. $POCl_3$ (2 ml) was slowly added to this solution. The solution was allowed to warm to room temperature and then added to a solution of (**14**) (800 mg) in dichloroethane (80 ml). The reaction mixture was stirred at 60°C for 4 h. The reaction was cooled to room temperature and 30% aq NaOAc (50 ml) was added and the reaction warmed to 50°C for 2 h. Dichloroethane layer was separated washed with water (2×100 ml), dried, and evaporated to dryness. The residue was chromatographed over silica gel (18″×1.5″). Eluted with 5% ethyl acetate/CH_2Cl_2 to recover unreacted (**14**) (440 mg). The column was then eluted with 10% ethyl acetate/CH_2Cl_2 and small fractions (25 ml) of the next red band were collected and analyzed by TLC. The first four fractions contained pure compound (**15**), were pooled and evaporated, 125 mg obtained. The last six fractions contained pure (**16**) were pooled and evaporated, 150 mg obtained.

(15). ^{1}H NMR ($CDCl_3$): δ 3.03 (t, 2H, CH$_2$CH_2CO$_2$CH$_3$), 3.08 (t, 2H, CH$_2$CH_2CO$_2$CH$_3$), 3.33, 3.34 (2s, 12H, CH_3), 3.67, 3.68 (2s, 12H, CO$_2$CH_3), 4.08 (dt, 4H, CH_2CH$_2$CO$_2$CH$_3$), 5.56 (dd, 1H, CH=C*H*CHO), 9.41 (s, 1H, *meso*-H), 9.44 (s, 2H, *meso*-H), 9.70 (d, 1H, C*H*=CHCHO), 9.91 (d, 1H, CH=CHC*H*O). HRMS: calcd: 820.2618; found: 820.2631.

(16). ^{1}H NMR ($CDCl_3$): δ 2.92 (m, 2H, CH$_2$CH_2CO$_2$CH$_3$), 3.07 (m, 2H, CH$_2$CH_2CO$_2$CH$_3$), 3.32, 3.35 (2s, 12H, CH_3), 3.66, 3.76 (2s, 12H, CO$_2$CH_3), 4.10 (dt, 4H, CH_2CH$_2$CO$_2$CH$_3$), 5.5 (dd, 1H, CH=C*H*CHO), 9.42 (s, 2H, *meso*-H), 9.43 (s, 1H, *meso*-H), 9.90 (d, 1H, C*H*=CHCHO), 9.91 (d, 1H, CH=CHC*H*O). HRMS: calcd: 820.2618; found: 820.2637.

Compound (19) and (20)

Compound (**16**) (100 mg) was dissolved in CH_2Cl_2 (2 ml) and phosphoric acid (2 ml) was added. When the compound had dissolved in acid layer, the CH_2Cl_2 was removed by rotoevaporation. The flask was then heated at 80°C for 4 h. The UV–Vis spectrum changed from a porphyrin to a Ni-benzochlorin (**17**) absorbing at 670 nm. The reaction was diluted with water (50 ml) and extracted with 10% pyridine/$CHCl_3$ (3×50 ml). The solvent was evaporated to dryness. Trimethylorthoformate (2 ml), methanol (2 ml) was added to the flask followed by conc. H_2SO_4 (0.2 ml) and the solution stirred overnight at room temperature. The reaction mixture was poured into 10% aqueous $NaHCO_3$ (10 ml) and extracted with CH_2Cl_2 (3×10 ml), dried over sodium sulfate, filtered and evaporated to dryness. The residue was precipitated from CH_2Cl_2/MeOH to give (**18**) (58 mg). Without further purification compound (**18**) was dissolved in methanesulfonic acid (2 ml) and heated at 80°C for 2 h. The reaction was diluted with water (10 ml) and extracted with CH_2Cl_2 (3×50 ml). The organic layer washed with 10% $NaHCO_3$ (1×10 ml) and water (1×10 ml), dried over sodium sulfate filtered and evaporated to dryness. The residue contained two products that were isolated by chromatography over silica gel, elution with 1–2.5% acetone/CH_2Cl_2. The first band isolated was compound (**19**) (11 mg, unoptimized), and the second band isolated was compound (**20**) (10 mg, unoptimized).

(19). UV–Vis ($CHCl_3$): λ max (ε) 411 (106000), 531 (11400), 565 (9200), 605 (7000), 659 (34700) nm. ^{1}H NMR ($CDCl_3$): δ 1.15 (m, 2H, CH_2CH$_2$CO$_2$CH$_3$ on the sp^3 carbon of the reduced pyrrole), 1.71 (s, 1H, N*H*), 1.96 (s, 3H, CH_3 on the sp^3 carbon of the reduced pyrrole), 2.17 (s, 1H, N*H*), 2.93 (m, 1H, CH$_2$CH_2CO$_2$CH$_3$ on the sp^3 carbon of the reduced pyrrole), 3.02 (m, 6H, CH$_2$CH_2CO$_2$CH$_3$ and 1H, CH$_2$CH_2CO$_2$CH$_3$ on the sp^3 carbon of the reduced pyrrole), 3.06, 3.15, 3.24 (3s, 9H, CH_3), 3.42, 3.65, 3.653 (3s, 9H, CO$_2$CH_3), 3.90 (t, 4H, CH_2CH$_2$CO$_2$CH$_3$), 4.10 (t, 2H, CH_2CH$_2$CO$_2$CH$_3$), 8.01(s, 1H, meso-H), 8.09 (m, 2H, exocyclic ring C*H*=CH–C*H*=), 8.56, 9.24 (2s, 2H, *meso*-H), 9.54 (dd, 1H, exocyclic ring CH=C*H*–CH=). HRMS: calcd: 748.3472; found: 748.3475.

(20). UV–Vis ($CHCl_3$): λ max (ε) 368 (49800), 404 (67000), 422 (63000), 588 (11900), 641 (14500), 700 (42000) nm. ^{1}H NMR ($CDCl_3$): δ 1.59 (s, 3H, CH_3 on the sp^3 carbon of the reduced pyrrole), 2.38 (m, 1H, exocyclic ring, CH_2CH$_2$CO), 2.91 (s, 3H, CH_3), 2.95 (m, 12H,

$CH_2CH_2CO_2CH_3$ and 1H, exocyclic ring, CH_2CH_2CO), 3.01 (s, 3H, CH_3), 3.19 (dd, 1H, exocyclic ring, CH_2CH_2CO), 3.24 (s, 3H, CH_3), 3.55 (m, 1H, exocyclic ring, CH_2CH_2CO), 3.59 (s, 3H, CO_2CH_3), 3.637, 3.644 (2s and m at the base, 6H, CO_2CH_3 and 2H, $CH_2CH_2CO_2CH_3$), 3.72 (t, 2H, $CH_2CH_2CO_2CH_3$), 3.90 (m, 2H, $CH_2CH_2CO_2CH_3$), 7.94 (dd, 1H, exocyclic ring –CH═C*H*–CH═), 8.00 (dd, 1H, exocyclic ring –CH═CH–C*H*═), 8.47, 8.94 (2s, 2H, *meso*-H), 9.21 (d, 1H, exocyclic ring –C*H*═CH–CH═). NH protons not observed. HRMS: calcd: 716.3210; found: 716.3214.

Acknowledgements

We thank Dr Jonathan C. Hanson for assistance with the crystallographic data collection. The work at Brookhaven was supported by the division of Chemical Sciences, US Department of Energy, under contract DE-AC02-98CH10886.

References

1. Kadish, K. M.; Smith, K. M.; Guilard, R. *The Porphyrin Handbook*; Academic: San Diego, 2000; Vol. 1–10; Sternberg, E. D.; Dolphin, D.; Bruckner, C. *Tetrahedron* **1998**, *54*, 4151.

2. Arnold, D. P.; Gaette-Holmes, R.; Johnson, A. W.; Smith, A. R. P.; Williams, G. A. *J. Chem. Soc. Perkin Trans. 1* **1978**, 1660.

3. Morgan, A. R.; Skalkos, D.; Maguire, G.; Rampresaud, A.; Garbo, G.; Keck, R.; Selman, S. H. *Photochem. Photobiol.* **1992**, *55*, 133.

4. Vicente, M. G. H.; Smith, K. M. *J. Org. Chem.* **1991**, *56*, 4407; Vicente, M. G. H.; Rezzano, I. N.; Smith, K. M. *Tetrahedron Lett.* **1990**, *31*, 1365; Robinson, B. C.; Morgan, A. R. *Proceedings of Optical Methods for Tumor Treatment and Detection: Mechanisms and Techniques in PDT V*; Dougherty, T. J., Ed.; SPIE, 1996; 191.

5. Robinson, B. C. Unpublished results.

6. Yashunsky, D. V.; Ponomarev, G. V.; Moskovkin, A. S.; Arnold, D. P. *Aust. J. Chem.* **1997**, *50*, 487.

7. Montforts, F.-P.; Zimmermann, G. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 458. Morgan, A. R.; Tertel, N. C. *J. Org. Chem.* **1986**, *51* (8), 1347.

8. Byrne, C. J.; Ward, A. D. *Tetrahedron Lett.* **1988**, *29*, 1421.

9. Single crystals of the title compound ($C_{42}H_{44}N_4O_7$) crystallized from CH_2Cl_2/MeOH in the triclinic space group $P\bar{1}$ with cell dimensions: a=7.020(3) Å, b=10.445(3) Å, c=25.406(8) Å, α=90.81(2)°, β=96.88(4)°, γ=104.25(4)°, V=1790.7(11) Å^3, and Z=2. Because of the small crystal size (0.225×0.088×0.025 mm), X-ray diffraction data were collected at the Brookhaven National Laboratory National Synchrotron Light Source at beamline X7B using a MAR345 image plate detector at λ=0.9432 Å, T=145 K (microcrystallography). Of the 20466 reflections measured ($\pm h \pm k \pm l$), 2352 were unique and 2000 had $I>2\sigma$. The structure was solved by direct methods and refined (based on F_2 using all data) by full matrix leastsquares methods (SHELXL-93). Final R factors for observed data are R=0.109 and $wR2$=0.294. Details and results of the experiment have been deposited at the Cambridge Crystallographic Data Centre.