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PREPARATION OF SUBSTITUTED CHLORINS AND BENZOCHLORINS

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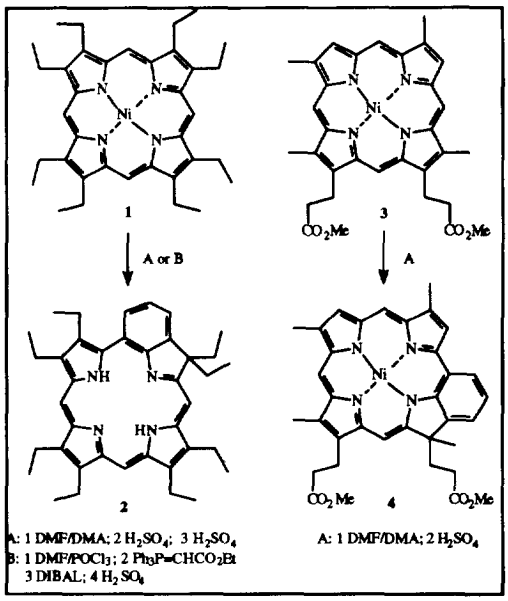
Abstract: The synthesis of functionalized benzochlorins has been achieved by cyclization of appropriately meso substituted porphyrins. Depending upon reaction conditions, a new class of chlorin derivatives can also be formed.

Interest in the synthesis and biological properties of benzochlorins has increased following reports that these porphyrin derivatives may have potential uses as photosensitizers in Photodynamic Therapy.[1-4] Improvements in the original synthesis of benzochlorins[5] have been described such that octaalkylbenzochlorins can be prepared in high yields from the corresponding porphyrins (e.g., **1**→**2**).[3,6-8] The synthesis of lipophilic derivatives, which may be of more interest from a biological viewpoint, has also been achieved by the use of unsymmetric porphyrins, such as deuteroporphyrin, as the reactant (e.g., **3**→**4**).[6] However, in this latter case, yields are low and complex mixtures have to be separated in order to isolate the desired product(s). We have taken a different approach for the preparation of benzochlorins containing polar substituents by introducing functionality through the benzochlorin moiety. Specifically, by reaction of a *meso* acrolein group (which forms the benzochlorin ring) with alkyl lithium reagents or a Wittig reagent prior to acid catalyzed cyclization, substituted benzochlorin rings can be formed and further modified to increase lipophilicity. Under certain reaction conditions, cyclization can also occur to generate a new class of chlorin derivative.



Thus, reaction of the acrolein **5**[6] with lithio ethyl acetate generated the corresponding β-hydroxy ester **6** in 90% yield. Treatment of **6** with concentrated sulfuric acid led to isolation of four products which were separated by column chromatography. Fraction 1 was shown to be the nickel chlorin **7**, isolated in 7% yield. Fraction 2, isolated in 10% yield proved to be the expected nickel benzochlorin **8** while fraction 3 (26%) was the corresponding metal-free derivative **9**. Finally, fraction 4 gave a 19% yield of the demetallated dehydration product **10**.

Changing the acid used in this reaction to trifluoroacetic acid led to a cleaner reaction with the nickel chlorin **7** being isolated in 60% yield. Under these reaction conditions, no benzochlorin analogs appeared to be formed. Since nickel porphyrins are not typically photoactive, it is important that removal of nickel from potential PDT agents be facile. We therefore examined demetallation of nickel complex **7** and found that treatment (of **7**) with concentrated sulfuric acid in methylene chloride for ten minutes gave the corresponding free-base derivative **11** in 18% yield. More prolonged treatment of **7** (neat sulfuric acid for three hours) however gave a different product distribution of 27% yield of benzochlorin **9** in addition to 41% of the *meso* vinylacrylate porphyrin **10**. This suggested that the initial chlorin **7** ring opened to form the corresponding vinylacrylate (**10**) which then recyclized to give the benzochlorin **9**. This was further demonstrated by reacting *meso* vinylacrylate porphyrin **10** itself with acid when it was shown that cyclization did indeed occur, producing the free base benzochlorin **9** in 70% yield. Although many PDT agents are used as the free base, others in clinical trials contain metals, in particular tin (tin

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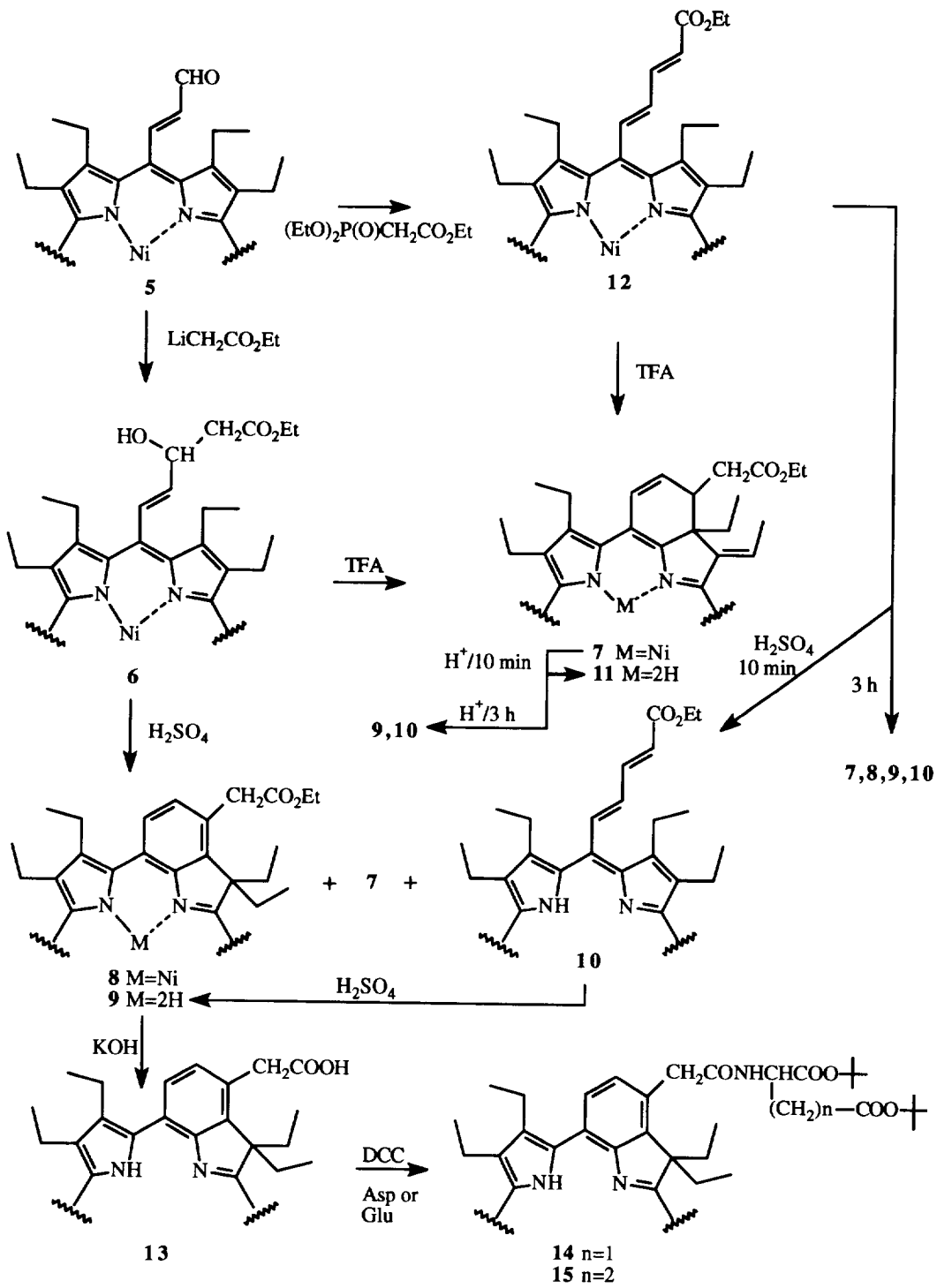
CHO
5
(EtO)2P(O)CH2CO2Et
CO2Et
12
LiCH2CO2Et
TFA
HO
CH
CH2CO2Et
6
TFA
CH2CO2Et
M
7 M=Ni
11 M=2H
H+/10 min
H+/3 h
9,10
H2SO4
10 min
3 h
7,8,9,10
H2SO4
CO2Et
NH
10
CH2CO2Et
+ 7 +
8 M=Ni
9 M=2H
H2SO4
KOH
CH2COOH
13
DCC
Asp or
Glu
CH2CONHCHCOO
(CH2)n—COO
14 n=1
15 n=2

ethyl etiopurpurin) and zinc (zinc phthalocyanine).[9] Consequently, the free base benzochlorin **9** was treated with either tin (II) chloride or zinc acetate to produce the corresponding metal derivatives.

The visible spectra of all cyclization products were as expected. Thus the free base benzochlorin **9** had a Q band absorption at 658nm which is consistent with that reported for the corresponding unsubstituted analog.[3] The presence of metals has also been reported to result in a red shift in the Q band rather than the blue shift typically observed with chlorophylls and simple chlorin systems. In the present case, the nickel, tin and zinc derivatives showed similar spectroscopic characteristics with maximum absorption bands at 672, 692 and 674nm respectively. Conversely, the chlorin **11** absorbed maximally at 688nm, red shifted from the typical chlorin absorption at 660nm due to the presence of the ß-pyrrolic ethylidene group. The presence of nickel produced a blue shift to 644nm, thus these chlorin derivatives behave as traditional chlorins rather than as benzochlorin analogs.

In a second approach to the generation of functionalized benzochlorin derivatives, the acrolein **5** was also reacted with the Wittig reaction using sodium ethoxide/triethyl phosphonoacetate. The expected product **12** was isolated in 88% yield and then treated with acid to effect cyclization. Treatment with trifluoroacetic acid resulted in formation of the nickel chlorin **7** in good (80%) yield while treatment with sulfuric acid gave a more complex product distribution. At short time intervals (10 minutes) the metal free vinylacrylate **10** was isolated in 73% yield however at longer time intervals (3 hr) the product distribution included the nickel chlorin **7** (7%), nickel benzochlorin **8** (20%), free base benzochlorin **9** (16%) and free base vinylacrylate **10** (20%). This indicates at least two reaction pathways, one involving initial cyclization to generate either the nickel chlorin **7** or the nickel benzochlorin **8** and perhaps subsequently the free base benzochlorin **9** and a second pathway involving initial demetallation to produce the vinylacrylate **10**, followed by cyclization to form free base benzochlorin **9**.

In order to demonstrate the further potential of this methodology to produce lipophilic benzochlorin derivatives, the benzochlorin **9** was subjected to base hydrolysis to generate the corresponding acid **13** in almost quantitative yield (95%). Since amino acids such as aspartate have been used previously to generate lipophilic PDT sensitizers (e.g., mono aspartyl chlorin e6 is currently in clinical trials),[9] the derivatization of benzochlorin **13** by both aspartate and glutamate was studied. Thus, condensation of **13** with the di-*t*-butyl ester of either L-aspartic acid or L-glutamic acid resulted in isolation of the corresponding adduct in 17% yield (aspartate **14**) and 20% yield (glutamate **15**). Cleavage of the di-*t*-butyl ester (e.g., of **15**) with TFA at room temperature then generated the corresponding diacid.

In summary, substituted chlorins and benzochlorins with spectroscopic properties suitable for use in photodynamic therapy can be prepared by a number of routes and are amenable to further derivatization. Yields of the free base benzoporphyrin from the reactant meso acrolein porphyrin **5** approach 45% using the route **5→12→10→9** while slightly lower yields of the chlorin derivative **11** can be obtained through the route **5→12→7→8**. Sufficient quantities of these materials are therefore available for further chemical manipulations and biological testing.[10]

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10. **analytical data for key compounds:** all NMR assignments were confirmed using C-13, ^1H 2D COSY and ^1H, ^{13}C HETCOR spectroscopy. For **6**: ^1H NMR ($CDCl_3$) δ 9.62 (s, 2H, 2 meso H), 9.60 (s, 1H, meso H), 9.30 (d, 1H, C<u>H</u>=CH), 5.04 (m, 1H, C<u>H</u>OH), 4.99 (dd, 1H, CH=C<u>H</u>), 4.27 (q, 2H, OCH_2), 3.91-4.07 (m, 16H, 8 x CH_2), 3.61 (d, 1H, OH), 2.68 (m, 2H, CH-C<u>H</u>$_2$), 1.88-1.97 (m, 24H, 8 x CH_3), 1.34 (t, 3H, $OCH_2C\underline{H}_3$). UV/vis λ 406, 530, 562 (ε 145979, 8574, 13166), Anal. Calc. $C_{43}H_{54}N_4O_3Ni$: C: 70.46, H: 7.43, N: 7.65; Found: C: 70.38, H: 7.54, N: 7.58. Mass spectrum, Calc. m/e 732, Found (FAB) 732. For **9**: ^1H NMR ($CDCl_3$) δ 9.50 (d, 1H, C<u>H</u>=CH), 9.20, 8.54, 7.98 (3s, 3H, 3 x meso H), 7.99 (d, 1H, CH=C<u>H</u>), 4.43 (s, 2H, CH_2CO), 4.26 (q, 2H, OCH_2), 3.49-3.86 (m, 12H, 6 x CH_2), 2.86, 2.71 (2m, 4H, CH_2 of *gem* diethyls), 1.59-1.84 (m, 18H, 6 x CH_3), 1.29 (t, 3H, $OCH_2C\underline{H}_3$), -0.04 (t, 6H, CH_3 of *gem* diethyls). UV/vis λ 412, 508, 562, 606, 658 (ε 125010, 7827, 9995, 11862, 33998), Anal. Calc. $C_{43}H_{52}N_4O_2.0.25H_2O$ C: 77.84, H: 8.29, N: 8.45; Found C: 77.91, H: 8.36, N: 8.45. Mass spectrum, calc. m/e 658, Found (DIP) 659 (M+1). For **10** ^1H NMR ($CDCl_3$) δ 10.08 (s, 2H, meso), 9.91 (s, 1H, meso), 9.60 (d, 1H, δ–H of vinylacrylate), 8.03 (dd, 1H, β-H of vinylacrylate), 6.51 (dd, 1H, γ-H of vinylacrylate), 6.02 (d, 1H, α-H of vinylacrylate), 4.33 (q, 2H, OCH_2), 3.93-4.08 (m, 16H, 8 x CH_2), 1.65-1.92 (m, 24H, 8 x CH_3), 1.38 (t, 3H, $OCH_2C\underline{H}_3$). UV/vis λ 408, 506, 540, 578, 628 (ε 161036,13533, 7091, 7071, 2826). Anal. calc. $C_{43}H_{52}N_4O_2$ C: 78.37, H: 8.27, N: 8.51; Found C: 78.03, H: 8.19, N: 8.16. Mass spectrum, Calc. m/e 658, Found (FAB) 660 (M+2). For **11** ^1H NMR ($CDCl_3$) δ 9.62, 9.55, 9.41 (3 s, 3H, 3 x meso H), 8.51 (dd, 1H, C<u>H</u>=CH), 6.63 (q, 1H, C<u>H</u>-CH_3), 6.22 (dd, 1H, CH=C<u>H</u>), 4.39 (q, OCH_2), 4.04 (m, 1H, CH), 3.80-4.05 (m, 12H, 6 x CH_2), 3.55 (dd, 1H, one H of sp^3 CH_2), 3.10 (dd, 1H, one H of sp^3 CH_2), 2.81 (d, 3H, $CHC\underline{H}_3$), 2.49 (m, 2H, CH_2CO), 1.74-1.90 (m, 18H, 6 x CH_3), 1.41 (t, 3H, $OCH_2C\underline{H}_3$), -0.043 (t, 3H, CH_3), -1.40, -1.99 (2s, 2H, 2 x NH). UV/vis λ 428, 520, 566, 628, 688 (ε 91805, 6343, 6013, 4313, 12806). Mass spectrum: Calc m/e 658, Found (FAB) 660 (M+2). For **12** ^1H NMR ($CDCl_3$) δ 9.42 (2s, 2H, 2 x meso H), 9.40 (s, 1H, meso H), 9.18 (d, 1H, ∂-H of vinylacrylate), 7.72 (dd, 1H, ß-H of vinylacrylate), 5.70 (dd, 1H, α–H of vinylacrylate), 5.52 (d, 1H, γ-H of vinylacrylate), 4.24 (q, 2H, OCH_2), 3.78-3.83 (m, 16H, 8 x CH_2), 1.69-1.80 (m, 24H, 8 x CH_3), 1.33 (t, 3H, $OCH_2C\underline{H}_3$). UV/vis λ 404, 530, 562 (ε 120996, 12211, 18316). Anal. Calc. $C_{43}H_{52}N_4)_2Ni.0.5H_2O$: C: 71.33, H: 7.38, N: 7.74. Found C: 71.00, H: 7.34, N: 7.84. Mass spectrum: Calc. m/e 714, Found (DIP) 715 (M+1). For **13**, ^1H NMR ($CDCl_3$) δ 9.52 (d, 1H, C<u>H</u>=CH), 9.21, 8.56, 7.98 (3s, 3H, 3x meso-H), 8.00 (d, 1H, CH=C<u>H</u>), 4.50 (s, 2H, C<u>H</u>$_2$-CO), 3.50-3.86 (m, 12H, 6 x CH_2), 2.18 (s, 2H, NH), 2.83, 2.71 (m, 2H each, CH_2 of *gem* diethyls), 1.63-1.82 (m, 18H, 6 x CH_3), -0.03 (t, 3H, CH_3 of *gem* diethyls). UV/vis λ 412, 528, 562, 606, 658 (ε 147205, 8861, 11437, 13473, 37490). Anal. Calc. $C_{41}H_{50}N_4O_2$:0.25H_2O C: 77.49, H: 8.02, N: 8.82. Found C: 77.55, H: 7.99, N: 8.47. Mass spectrum, Calc. m/e 630, Found (DIP) 586 (M-CO_2^-). For **14**, ^1H NMR ($CDCl_3$) δ 9.54 (d, 1H, C<u>H</u>=CH), 9.20, 8.54, 7.96 (3s, 3H, 3 x meso H), 7.98 (d, 1H, C<u>H</u>=CH), 6.75 (d, 1H, NH of asp), 4.80 (m, 1H, NHC<u>H</u>), 4.50, 4.40 (2d, 1H each, C<u>H</u>$_2$CO), 3.48-3.85 (m, 12H, 6 x CH_2), 2.60-2.88 (m, 6H, ß-CH_2 of asp and 2 x CH_2 of *gem* diethyl), 1.60-1.82 (m, 18H, 6 x CH_3), 1.36, 1.06 (2s, 9H each, 2 x *t*-butyl), -0.05 (t, 6H, CH_3 of *gem* diethyl). UV/vis λ 412, 530, 562, 606, 658 (ε 160390, 13750, 16606, 18520, 43928), Mass spectrum, Calc. m/e 858, Found (FAB) 858.

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