

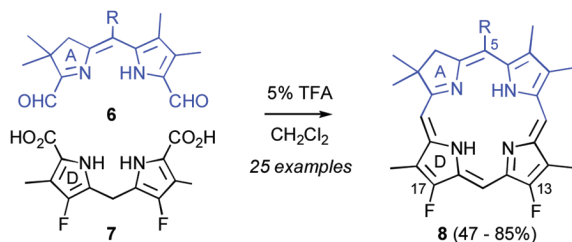
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Studies in Chlorin Chemistry. III. A Practical Synthesis of C,D-Ring Symmetric Chlorins of Potential Utility in Photodynamic Therapy

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Abstract



C,D-Ring symmetric chlorins **8** were prepared in 47-85% yield, on scales up to several hundred milligrams, by condensation of appropriately substituted *bis*-formyldihydro-dipyrriins **6** and dihydropyrromethane *bis*-carboxylic acids **7** in 5% TFA/CH₂Cl₂ (25 examples). Target chlorins were chosen to systematically probe the effect of lipophilic and hydrophilic substituents on tissue partitioning and cellular membrane penetration in photodynamic therapy (PDT).

Introduction

The chlorins are a class of 18 π -electron aromatic tetrapyrroles formally derived from porphyrins by saturation of a peripheral double bond (cf. ring A, Figure 1). Chlorophyll a (**1**, R = phytyl) is the most ubiquitous example, serving as a light harvesting chromophore in photosynthetic plants, algae, and cyanobacteria (certain bacteriochlorophylls perform a similar function in phototrophic bacteria).¹ However, a number of lesser known chlorins also play important biological roles. Cyclophorbide (**2**) and related species are thought to inhibit damaging oxidative processes in certain marine species, including *Darwinella oxeata* (a sponge), the short-necked clam *Ruditapes philippinarum* and the scallop *Patinopecten yessoensis*.² Also, the structurally unique chlorin bonellin (**3**) is a hormone responsible for sexual differentiation in the marine worm *Bonella viridis*.³ Finally, in addition to their natural functions synthetically derived chlorins have attracted significant attention in both medical and materials sciences. Due to their favorable photophysical properties chlorins show promise in tumor photodynamic therapy (PDT), a technique that employs photostimulated production of singlet oxygen to selectively eradicate malignant tissue.⁴ In a relatively new area of exploration materials engineers have studied this ring system as a chromophore in artificial photosynthesis.⁵

Most *de novo* syntheses of chlorins are modeled on the methodology of Battersby^{6a} and Montforts,^{6b} involving either photochemical or alkali induced ring closure of properly substituted linear tetrapyrroles **4** (Scheme 1; X = OMe, Br, etc.).⁷ Tetrapyrroles **4** are derived

from simpler ring systems employing techniques such as sulfide contraction,^{6b,8} thio-Wittig reaction,⁹ and reductive cyclization of pyrrole-substituted nitroketones.¹⁰ While elegant in concept the cyclization of **4** to **5** can be problematic and is typically carried out on small scales, employing metal templates, and affording **5** in modest - good yields.^{6,8}

In 2001 we described in communication form a new synthesis of chlorins based upon a variant of the MacDonald porphyrin synthesis, involving condensation of *bis*-formyl-dihydrodipyrrens **6** with symmetrical dipyrromethanes **7** (Scheme 2).¹¹ Simple dissolution of **6** and **7** in neat TFA was found to afford chlorins **8** in 35-45% yield with no special precautions against air or light and without metal complexation. A key feature of this approach is that the chlorin chromophore is obtained directly in the proper oxidation state and with no need for subsequent isomerization. We believe this characteristic accounts in large part for the simplicity of the experimental conditions. Since dipyrromethanes of type **7** are readily available,¹² we have devoted much effort since our original paper developing improved synthetic routes to A,B-ring dialdehydes **6**, incorporating diverse substituents A-D and in particular *meso*-groups R (C₅ in **8**). Typically *meso*-substituents have been the most challenging to introduce employing existing methodology, which is unfortunate since their properties can significantly influence tissue partitioning in PDT.¹³ In this paper we describe versatile new syntheses of these materials as well as greatly improved conditions for their conversion to C,D-ring symmetric chlorins **8**.

Results and Discussion

I. Synthesis of *bis*-Formyl Derivatives **6**

Method A—Our original route to *bis*-formyl-dihydrodipyrrens **6** built upon the ready availability of enolactones **11**, prepared in 70-96% yield from alkyne acids **9** and iodopyrroles **10** (Scheme 3).¹¹ Lactones **11** were then converted to *E,Z*-mixtures of thioimidates **12** by a three step sequence consisting of (1) aminolysis, (2) thiolactam formation, and (3) concomitant decarboxylative formylation/S-methylation employing trimethylorthoformate (TMOF) in neat TFA.^{9b} We intended to convert both isomers of **12** to the corresponding dihydrodipyrrens **13** by transition metal-catalyzed methylation. In practice this transformation worked well with *Z*-thioimidates **12-Z** employing the reagent system Pd(0)/MeZnI. The resulting *Z*-dihydrodipyrrens **13-Z** were then oxidized in good yield to the desired diformyl derivatives **6**. Surprisingly, however, the corresponding *E*-thioimidates **12-E** were unreactive toward methylation using Pd(0)/MeZnI and most other commonly employed cross-coupling techniques (trace quantities of **13** were produced with Ni(II) catalysts). Eventually this difference was traced to a selective activating effect of Zn, which serves to polarize the thioimide C-S bond in **12-Z** by chelation.¹⁴ In the event this reactivity pattern had far reaching consequences, since the ratio of **12-Z**:**12-E** decreased dramatically with increasing size of R (*i.e.* H > Me ≫ Ph), making it impractical to incorporate larger *meso*-substituents. Because of this we were able to prepare only a very limited number of chlorin precursors **6**.

Method B—Subsequently we found that lactones **11** undergo clean condensation with the Petasis reagent (TiCp₂Me₂), affording high yields of enol ethers **14** incorporating a wide range of *meso*-substituents R (Scheme 4).¹⁵ This discovery provided the basis for a very streamlined synthesis of dihydrodipyrrens **15**, which were formed in “one pot” by hydrolysis of **14** to the corresponding diketones, followed by condensation with an appropriate ammonia source. Importantly, the Petasis reagent was compatible with commonly occurring functional groups such as propionate esters (D = CH₂CH₂CO₂Me), as well as regioisomeric substitution patterns in ring A (A,B = di-Me, di-H). Although prepared in a different context dihydrodipyrrens **15** were also attractive precursors to diformyl derivatives **6**, via decarboxylative formylation to give the previously employed intermediates **13**. As in Scheme 3 we expected this

transformation to be straightforward, involving pre-treatment of **15** with TFA followed shortly thereafter with TMOF (*conditions i*). Unexpectedly, though, this seemingly well-precedented step proved to be highly capricious, affording **13** in yields ranging from 8% to 69% depending partly upon the nature of *meso*-substituents R. Only with R = H were we able to obtain reproducible yields in the range of ~70%. In part this behavior may be due to competitive protonation at the basic pyrroline ring nitrogen in **16**, thereby inhibiting decarboxylation and/or formylation (i.e., **16-H+** → **17-H+** → **13**). Battersby et al. experienced similar difficulties with a closely related ring system during the course of a synthesis of bonellin (**3**).^{10c}

We explored many approaches for improving the conversion of **15** to **13**, initially employing *meso*-phenyl substrate **15a** in combination with variants of the standard protocol (TFA/TMOF, Scheme 5).¹⁶ As above, these experiments gave erratic yields of the desired formylated compound **13a** accompanied by significant decomposition. In most cases the only identifiable by-product was the trifluoromethyl ketone **18a** (13-18%). Interestingly, we could find no trace of the presumed intermediates **16a** and **17a** in the crude reaction mixtures, and it remains an open question whether formylation precedes or follows decarboxylation. Battersby et al. also observed trifluoromethyl ketone formation in their studies cited above,^{10c} but the origin of this compound was not investigated. In the case of ketone **18a** two observations provided insight into this question. First, **15a** gave essentially identical yields of **18a** upon treatment with TFA alone, seemingly eliminating any mechanistic role for TMOF in the formation of this compound. Second, **17a** prepared independently (*vide infra*) reacted only very slowly with TFA under conditions that led to rapid conversion of **15a** to **18a**. Together these results suggest that a likely intermediate in the conversion of **15a** to **18a** is the mixed anhydride **19a**, which might be transformed to **18a** in either inter- or intramolecular fashion. In any event it was clear that decarboxylation of **15a** with TFA would inevitably lead to substantial loss of starting material to this side reaction.

In an effort to circumvent this problem we briefly explored the possibility of reversing the order of decarboxylative formylation and oxidation (Scheme 6). Our thought was that the electron withdrawing formyl group in **20a** would decrease the basicity of the pyrroline ring, thereby facilitating protonation of the pyrrole ring. However, although we obtained reasonable yields in the conversion of **15a** to **20a** (~65%), all attempts at decarboxylative formylation produced only the carboxylic acid **21a** along with decomposition products. Decarboxylation also failed with very strong acid combinations such as HBr/HOAc.¹⁷ These results are reminiscent of those observed with simple pyrrole carboxylic acids bearing electron withdrawing groups.¹⁸

In contrast to formyl derivative **20a**, the less electron deficient methylpyrroline **15a** underwent clean decarboxylation with HBr/HOAc, affording a 96% yield of the α -free pyrrole **17a** as a mixture of *Z*- and *E*-isomers (Table 1). With decarboxylation no longer an issue we examined a number of milder reagents for effecting the desired formylation of **17a** to **13a**. Of these, only the Vilsmeier reagent (POCl₃/DMF) exhibited modest promise, affording a 43% yield of **13a** (*Z*-isomer only).¹⁹ Employing TMOF/TFA the yields of **13a** were actually lower than those obtained by direct decarboxylative formylation of **15a** to **13a** (*vide supra*). Mainly this was because **17a** was unstable to prolonged exposure to TFA. In experiments to minimize this problem we found that **13a-Z,E** was obtained in 73% yield when a solution of crude **17a** in CH₂Cl₂/triethylorthoformate (TEOF) was added to pre-cooled TFA (*conditions ii*). These conditions provided reproducible results and were also satisfactory for preparing formyl derivatives **15d** (R = C₅H₁₁, 57%) and **15e** (R = C₁₀H₂₁, 61%). However, for substrates bearing small *meso*-substituents even these conditions proved to be too harsh (**15b,c**).

Method C—In parallel studies we were exploring a third strategy for synthesizing **13** that provided additional flexibility. Based on mechanistic considerations we expected that

enolactones **11** would be good substrates for decarboxylative formylation, since in these compounds there is no pyrroline ring to compete for protonation (*Method C*, Scheme 7). In agreement, **11** routinely afforded 75-95% yields of formyl derivatives **22** with TEOF/TFA (*E*-isomers only). We further hoped that **22** might undergo a selective Petasis reaction at the lactone carbonyl group, as previously observed with ester-lactones **11** (cf. Scheme 4). However, all attempts at effecting this conversion produced complex mixtures. Previously we had examined the ring opening of ester-lactones **11** with alkyl lithium species Li-Nu, but in most cases were unable to prevent multiple addition (an exception was LiCH₂TMS, which is very sterically hindered).¹⁵ Nevertheless we attempted the same transformation with formyl-lactones **22** and were pleased to find that these species underwent selective ring opening with a variety of nucleophiles Li-Nu (**22** → **23** → **24**). Of particular interest, reaction of **22c** with lithiodithiane (Li-**B**) cleanly produced the protected glyoxaldehyde derivative **24cB** (74%), while lithioanisole (Li-**C**) gave a 78% yield of ring-opened species **24bC**. Both **24cB** and **24bC** held out the possibility of attaining the desired oxidation state of **6** directly.²⁰ Even Li-Me (Li-**A**), possessing little if any steric hindrance, showed excellent chemoselectivity, affording 74-80% yields of **24aA-eA** upon slow addition at -78° C. At present we have no rigorous explanation for this selectivity, although it is likely that the acidic pyrrole N-H group plays a role both in protecting the formyl group and in preventing multiple addition (two equivalents of Li-Nu are required for complete reaction). As a working hypothesis we suggest that the C-4 ketone deriving from **22** is stabilized in a chelated structure of type **23**, maintaining the enolate tautomer until acid workup.

Unfortunately we were unable to effect the desired ring closure of diketones **24cB** or **24bC** despite intensive efforts over a period of many months (Scheme 8). Dithiane **24cB** was typically recovered intact following aminolysis, most likely due to steric hindrance at the C-1 carbonyl group (X-ray analysis subsequently confirmed this suspicion; cf. Scheme 8 and Supporting Information). In contrast, thioanisole derivative **24bC** underwent rapid aldol condensation to cyclopentenone **25** under mildly basic conditions (83%), reflecting the increased acidity of the C-20 methylene protons (chlorin numbering).

Even simple diketone derivatives **24a-e** presented a number of hurdles to cyclization, partly because of the presence of the very sensitive formyl group (Scheme 9). Formylpyrroles as a class are generally unstable to acids,²¹ a property that was especially pronounced with **24a-e**. These substrates underwent rapid decomposition with even weakly acidic ammonium salts. In contrast, basic or neutral sources of ammonia cleanly afforded mixtures of hemiaminal intermediates **26**, but these species were resistant to dehydration and easily reverted to diketones **24**. Working with substrate **24b** (R = Me) we eventually found that the combination of (NH₄)₂CO₃/basic Al₂O₃ in CH₃CN at 75 °C gave ~75% yields of the corresponding dihydrodipyrin **13b**, a significant improvement over *Method B* (cf. Table 1). In analogous fashion diketone **24d** (R = *n*-pentyl) afforded **13d** in much improved yield (77%). However, the relatively unhindered substrate **24c** (R = H) required special care. This material was susceptible to competing aldol condensation, and upon aminolysis at 75 °C gave predominantly the aldol product **27c** (51%) along with only 18% of dihydrodipyrin **13c**. After further experimentation we found that the aldol pathway was greatly reduced by effecting aminolysis at RT for 24 hrs before briefly heating to 75°C, affording **13c** in 58% yield along with 17% of **27c**. However, **13c** was still best prepared using *conditions i* (cf. Scheme 4). Finally, we were surprised to find that the *meso*-Ph diketone **24a** underwent significant decomposition upon attempted aminolysis, since in related examples the Ph-substituent appeared to have a stabilizing influence.¹⁵ In any event dihydrodipyrin **13a** was best prepared using *conditions ii*, as was the *n*-decyl derivative **13e** (cf. Table 1). All of these results are summarized in Scheme 10. Because of the unpredictable effect of *meso*-substituents R on substrate reactivity/stability a truly general synthesis of formyl derivatives **13** remains elusive. However, this investigation

culminated in two complementary routes to these key intermediates that together are far more efficient than our original approach.¹¹

Oxidation of Pyrrolines 13 to bis-Formyl-dihydrodipyrrens 6—In our original studies we carried out the conversion of formyl-dihydrodipyrrens **13a-c** to dialdehydes **6a-c** by oxidation with selenium dioxide (cf. Scheme 3).¹¹ While this procedure generally gave satisfactory yields of **6a-c**, the final products were invariably contaminated with selenium metal that was very difficult to separate. Among other consequences this made obtaining accurate analytical data difficult and no doubt also impacted on subsequent steps. Because of this we spent considerable time exploring other means of accomplishing the desired oxidation. The literature contains many examples of similar oxidations employing a wide variety of reagents. Of these we screened 15-20 procedures that appeared to offer the most promise (see reference 22 for a complete listing).²²⁻²⁴ Generally speaking these fell into three categories: (1) direct oxidation using powerful reagents of the Cr(VI), Co(II), Cu(II), and Pb(IV) families;²³ (2) oxidation initiated by *bis*-halogenation (NCS, NBS, SOCl₂, etc.) followed by hydrolysis;²⁴ and (3) methyl anion generation followed by *in situ* capture with oxidants including diselenides, disulfides, NBS, etc.^{24b} In several cases we examined both stoichiometric and catalytic variants of the literature procedures. The results were uniformly discouraging, with some reagents exhibiting little reactivity while others caused rapid decomposition (Scheme 11). Ultimately we returned to the SeO₂ procedure, exploring the effect of reagent purity, additives, and co-oxidants. To summarize briefly, freshly sublimed SeO₂ provided no apparent advantage,²⁵ nor did so-called “wet” solvents described in the literature as having beneficial effects (in our case even trace amounts of water accelerated decomposition).²⁶ We did, however, observe very clean reactions using dry CH₂Cl₂ as solvent with 1-2 equivalents of pyridine as additive (the rate accelerating effect of pyridine is well documented).²⁶ Employing **13b** (R = Me) as a substrate we consistently obtained yields of **6b** in the range of 65-70% following this protocol. While promising, though, ICP-MS analysis indicated that the product was still contaminated with up to 0.61% by weight (2 mol%) selenium. At this time we became aware of a report describing the removal of colloidal selenium by brief heating in DMF, which produces a black metallic allotrope that can be easily removed by filtration.²⁷ When this step was applied to the crude oxidation product prepared as above, the resultant precipitate was easily removed, the overall yield remained essentially the same, and **6b** was obtained in a high state of purity. In analogous fashion diformyl derivatives **6a-e** were prepared in 60-70% yield without further optimization.

II. Chlorin Formation

The experiments described above, while affording *bis*-formyl-dihydrodipyrrens **6** in much improved yields, would be of lesser value if the final condensation of **6** and dipyrromethanes **7** to give chlorins **8** were not of comparable efficiency. Our original conditions for this reaction called for dissolution of **6** and **7** in neat TFA, which was deemed necessary to initiate decarboxylation of **7** to the presumably more reactive α -unsubstituted derivatives (*conditions a*, cf. Scheme 2).¹¹ This protocol afforded 35-45% yields of a limited number of chlorins **8**. However, with greater quantities of **6** available, we began more detailed studies that revealed that our assumption pertaining to decarboxylation was not valid.

As representative substrates we first examined the stability of dihydrodipyrin **6b** and dipyrromethane **7b** in neat TFA, now aware of the potential side reactions that this solvent might induce (Scheme 12). Under these conditions **6b** decomposed within minutes at ambient temperature. Dipyrromethane **7b** afforded moderate yields of the *bis*-decarboxylated product **29b** along with significant quantities of trifluoroacylated derivative **28b**,²⁸ mirroring our experience with dihydrodipyrrens **15** outlined in Scheme 5. Interestingly, though, isolated and purified dipyrromethane **29b**, for which we expected trifluoroacylation to be minimized (vide

supra), gave *lower* yields of chlorin **8bb** than dicarboxylic acid **7b** under otherwise identical conditions (33% vs 42%). To explore this result further we screened numerous solvent and acid combinations with **29b**, including such Lewis acids as TiCl₄, BF₃, and Sc(OTf)₃ that have been successfully employed in similar condensations.²⁹ In the present case these catalysts caused significant decomposition and little or no chlorin **8bb** could be detected by TLC and/or UV analysis. More promising results were obtained with Bronsted acids, in particular TsOH in MeOH/CH₂Cl₂ (*conditions b*),³⁰ although these conditions proved unreliable for larger scale syntheses of **8bb**. Based on these experiments it appeared that decarboxylation was at the least not a prerequisite to chlorin formation, raising the possibility that dicarboxylic acid **7b** might be a superior condensation partner under more refined conditions. Working from this premise we eventually identified the combination of 5% TFA in CH₂Cl₂ as a particularly effective medium for condensation,³¹ affording chlorin **8bb** in a remarkably high state of purity following washing with either 3M NH₄OH or saturated KHCO₃ (*conditions c*). Final purification was by silica gel chromatography, which consistently afforded 65-75% yields of **8bb** on scales up to several hundred milligrams (typically, however, reactions were run on 25-50 mg scale for convenience). In analogous fashion we prepared chlorin derivatives **8aa** - **8ee** bearing lipophilic substituents ranging up to *n*-decyl at C₅, along with aliphatic esters of chain length 2-10 at C₁₃ and C₁₇ (Table 2; the potential usefulness of a carboxylate functionality is described below). Yields employing *conditions c* ranged from 47-85% and are shown in bold. Where applicable yields employing *conditions a* and *b* are also included.

An important component of these studies was to prepare C,D-ring symmetric chlorins **8** of a substitution pattern that could be useful in probing structure-activity relationships in photodynamic therapy (PDT, *vide supra*). It has been known for many years that lipophilic substituents can exert a strong influence on such critical parameters as drug uptake, intracellular location and photosensitizing efficacy.¹³ Moreover, as recently shown by Ehrenberg et al.,³² carboxylate “anchors” of the type incorporated in rings C and D in **8** might be tailored in length to either minimize or maximize cellular membrane penetration, and thus overall exposure to photogenerated ¹O₂ (Figure 2). Chlorins **8aa-ee** in Table 2, incorporating both a lipophilic “head” and a hydrophilic “tail”, provide an attractive starting point for testing this hypothesis. Finally, the described methodology should also be suitable for preparing chlorins of potential interest in materials science. It is worth noting, though, that with C,D-ring symmetric chlorins **8** our synthetic objectives were simplified by the fact that it was not necessary to differentiate either the formyl groups in **6** or the α -pyrrole positions in dipyrromethanes **7**. The application of this “2 + 2” strategy to the synthesis of unsymmetrical chlorins presents additional challenges that will be the subject of a forthcoming paper.

Experimental Section

Representative procedures for the synthesis of chlorins **8**

5-[1-(4,4-Dimethyl-5-oxo-dihydro-furan-2-ylidene)-ethyl]-3,4-dimethyl-1H-pyrrole-2-carbaldehyde (22b)—TFA (8.80 mL, 118 mmol) was added to **11b** (1.0 g, 3.0 mmol) under a nitrogen atmosphere, and the solution was stirred vigorously for 5 min. The reaction was cooled to 0°C for 10 min and then treated with triethylorthoformate (2.7 mL, 16.4 mmol). After 20 min, the reaction was poured into 10% aq KH₂PO₄ (40 ml) at 0°C and extracted with CH₂Cl₂ (3 × 15 ml). The combined organic extracts were washed sequentially with water and saturated aq NaHCO₃, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, EtOAc:hexanes = 3:7) to give **22b** (695 mg, 89%) as a colorless crystalline solid, mp 172.5-174 °C. *R_f* (4:6 EtOAc/hexanes) 0.41; IR (thin film) 3253, 1799, 1700, 1628, 1079 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.27 (s, 6H), 1.91 (s, 3H), 2.01 (t, J=1.71, 3H), 2.27 (s, 3H), 2.58 (q, J=1.71, 2H), 9.54 (s, 1H), 9.74 (br s, 1H); ¹³C NMR (500 MHz, CDCl₃) δ 9.2, 9.7, 16.1, 25.0, 40.5, 40.5, 104.9, 119.2, 129.2, 132.5, 136.3, 146.7,

177.0, 180.0. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36; O, 18.37. Found: C, 68.54; H, 7.28; N, 5.33.

3,4-Dimethyl-5-(1,4,4-trimethyl-2,5-dioxo-hexyl)-1H-pyrrole-2-carbaldehyde (24b)—A solution of **22b** (1.77 g, 6.77 mmol) in THF (130 mL) was cooled to -78°C and treated dropwise with 1.6M MeLi in Et_2O (8.40 mL, 13.5 mmol) over 20 min. The reaction was then quenched by addition to 200 mL of saturated aq NH_4Cl . After allowing the mixture to warm to rt, Et_2O (50 mL) was added and the layers were separated. The organic layer was washed sequentially with water and brine, dried over Na_2SO_4 , filtered and concentrated. The resulting yellow oil was purified by flash chromatography (silica gel, $\text{EtOAc}:\text{hexanes} = 3:7$) to give **24b** (1.50 g, 80%) as a colorless crystalline solid, mp $103\text{--}104^\circ\text{C}$. R_f (2:3 $\text{EtOAc}:\text{hexanes}$) 0.25; IR (thin film) 3253, 1706, 1628 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) 1.12 (s, 3H), 1.13 (s, 3H), 1.36 (d, $J=7.3$, 3H), 1.93 (s, 3H), 2.16 (s, 3H), 2.25 (s, 3H), 2.59 (d, $J=17.9$, 1H), 2.87 (d, $J=17.9$, 1H), 3.89 (q, $J=7.1$, 1H), 9.53 (s, 1H), 9.74 (br s, 1H); ^{13}C NMR (500 MHz, CDCl_3) δ 8.6, 9.0, 15.7, 25.1, 25.5, 25.7, 44.5, 45.9, 51.2, 118.5, 128.9, 132.4, 136.1, 176.8, 207.5, 213.3. HRMS (EI) Calcd for $C_{16}H_{23}NO_3$: 277.1678; found: 277.1678; Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05; O, 17.31. Found: C, 69.44; H, 8.35; N, 4.96.

3,4-Dimethyl-5-[1-(4,4,5-trimethyl-3,4-dihydro-pyrrol-2-ylidene)-ethyl]-1H-pyrrole-2-carbaldehyde (13b)—A solution of **24b** (1.35 g, 4.9 mmol) in CH_3CN (53 mL) was treated with $(\text{NH}_4)_2\text{CO}_3$ (4.6 g, 49 mmol) and basic alumina (6.7 g, Grade I), flushed with nitrogen, and heated to 75°C in a sealed flask for 8 hrs. At the end of this period, the mixture was cooled to rt, filtered, and concentrated. The residue was dissolved in CH_2Cl_2 , washed with water, dried over Na_2SO_4 , filtered and concentrated. The resulting oil was purified by flash chromatography (silica gel, $\text{EtOAc}:\text{hexanes} = 1:2$) to give **13b** (940 mg, 75%) as a crystalline solid, mp $156\text{--}157^\circ\text{C}$. R_f (1:2 $\text{EtOAc}:\text{hexanes}$) 0.27; IR (thin film) 3252, 1635, 1589 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) 1.20 (s, 6H), 2.11 (s, 3H), 2.16 (s, 3H), 2.17 (s, 3H), 2.26 (s, 3H), 2.58 (s, 2H), 9.58 (s, 1H), 11.77 (s, 1H); ^{13}C NMR (500 MHz, CDCl_3) δ 8.8, 11.2, 15.7, 17.9, 26.0, 43.8, 47.8, 113.3, 118.9, 128.3, 131.4, 136.9, 151.6, 176.0, 187.2. HRMS (EI) Calcd for $C_{16}H_{22}N_2O$: 258.1732; found: 258.1726; Anal. Calcd for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84; O, 6.19. Found: C, 74.41; H, 8.72; N, 10.78.¹¹

5-[1-(5-Formyl-4,4-dimethyl-3,4-dihydro-pyrrol-2-ylidene)-ethyl]-3,4-dimethyl-1H-pyrrole-2-carbaldehyde (6b)—A solution of **13b** (0.80 g, 3.1 mmol) in CH_2Cl_2 (62 mL) and pyridine (0.37 mL, 3.7 mmol) was treated with SeO_2 (0.41 g, 3.7 mmol) and stirred at rt for 2 h. The solvent was then removed by rotary evaporation, and the residue was redissolved in DMF (30 mL) and heated to 80°C for 15 min. The reaction mixture was cooled to rt, filtered, and poured into water (100 mL). The solution was extracted with CH_2Cl_2 (4×30 mL), and the combined organic extracts washed sequentially with saturated aq NaHCO_3 and brine, dried over Na_2SO_4 , filtered, and concentrated. The resulting oil was purified by flash chromatography (silica gel, $\text{EtOAc}:\text{hexanes} = 2:3$) to give **6b** (599 mg, 71%) as a yellow crystalline solid, mp $135\text{--}137^\circ\text{C}$. R_f (1:2 $\text{EtOAc}:\text{hexanes}$) 0.34; IR (thin film) 3302, 1687, 1635 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) 1.37 (s, 6H), 2.20 (s, 3H), 2.22 (s, 3H), 2.28 (s, 3H), 2.73 (s, 2H), 9.66 (s, 1H), 9.94 (s, 1H), 11.32 (br s, 1H); ^{13}C NMR (500 MHz, CDCl_3) δ 8.9, 11.8, 19.3, 26.1, 46.0, 46.3, 122.0, 125.3, 130.0, 131.2, 135.3, 152.0, 177.4, 177.5, 190.5; HRMS (EI) Calcd for $C_{16}H_{19}N_2O_2$: 271.1447; found: 271.1450; Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29; O, 11.75. Found: C, 70.45; H, 7.42; N, 10.12.¹¹

3-[18-(2-Methoxycarbonyl-ethyl)-3,7,8,10,13,13,17-heptamethyl-12,13,22,24-tetrahydro-porphin-2-yl]-propionic acid methyl ester (8bb)—Nitrogen was bubbled through a suspension of **6b** (201 mg, 0.74 mmol) and **7b** (321 mg, 0.74 mmol) in CH_2Cl_2 (67 mL) for 10 min. The mixture was treated with TFA (3.36 mL) and stirred at rt in the dark for

24 h. The reaction was then poured into 3M aqueous NH_4OH (30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined organic layers were washed sequentially with water and brine, dried over Na_2SO_4 , filtered, and concentrated. The residue was purified by flash chromatography (silica gel, EtOAc:hexanes = 1:5) to give **8bb** (313 mg, 70%) as a green crystalline solid that was identical to the literature compound.¹¹

Supporting Information Available

Refer to Web version on PubMed Central for supplementary material.

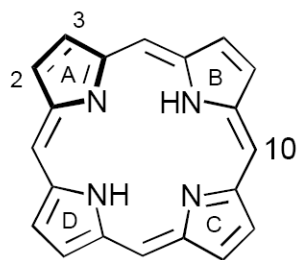
Acknowledgements

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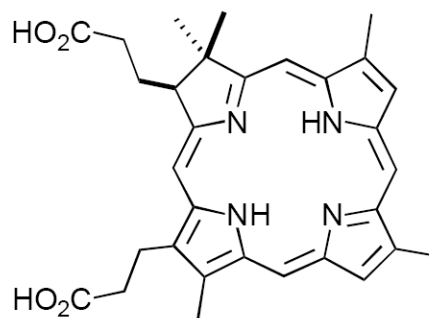
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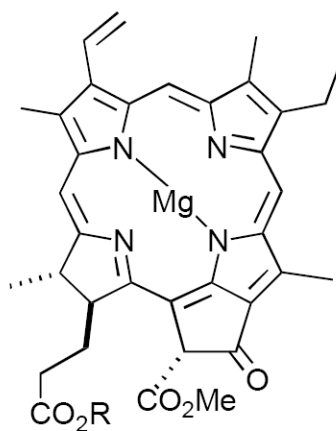
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 22. (a) Reagents that were screened include: PCC, PDC, CAN, DDQ, MnO₂, CrO₃, Pb(OAc)₄, Co(OAc)₂, CuI/TBHP, CuCl₂/TBHP, Pd/TBHP, Pd(OAc)₂/PhI(OAc)₂, (SePh)₂/PhIO₂, *t*-BuI/FeCl₂/DMSO, CuCl₂/LiCl, NCS/NBS, SO₂Cl₂. Leading references are included for certain reagents.
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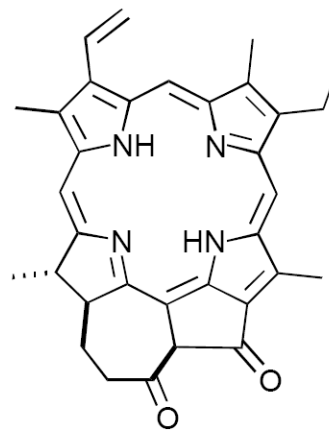
porphyrin (unsat'd C₂-C₃)
chlorin (sat'd C₂-C₃)



Bonellin (3)



Chlorophyll a (1)



Cyclophorbide (2)

FIGURE 1.
Some naturally occurring chlorins

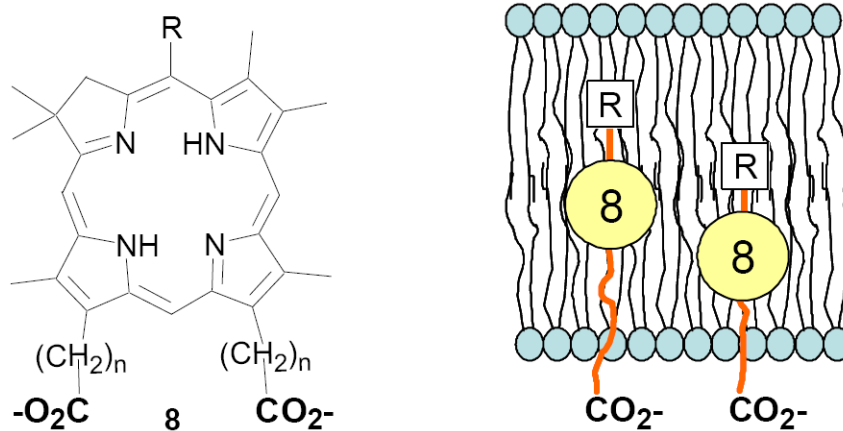
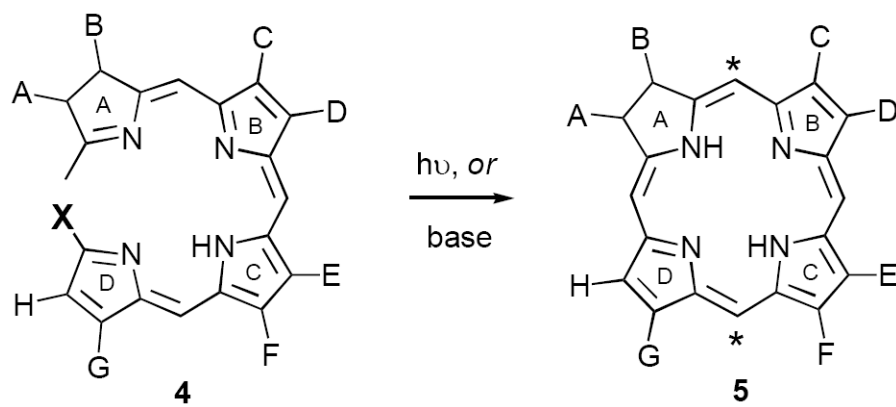
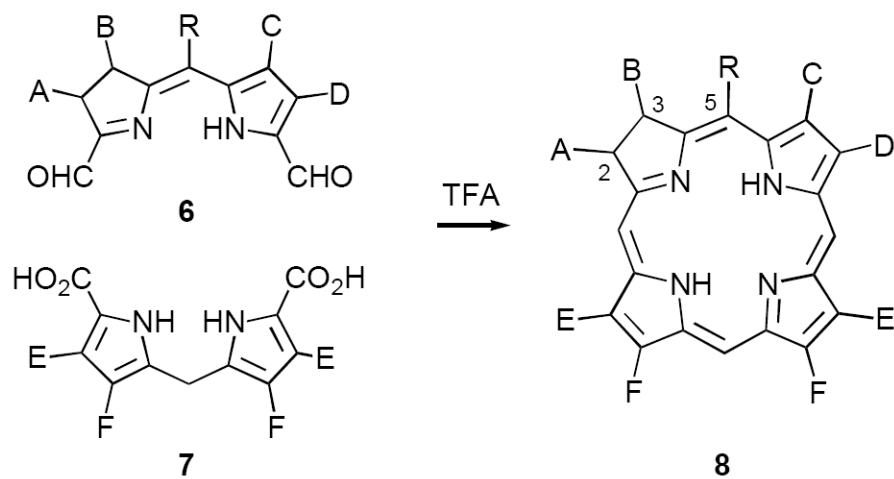


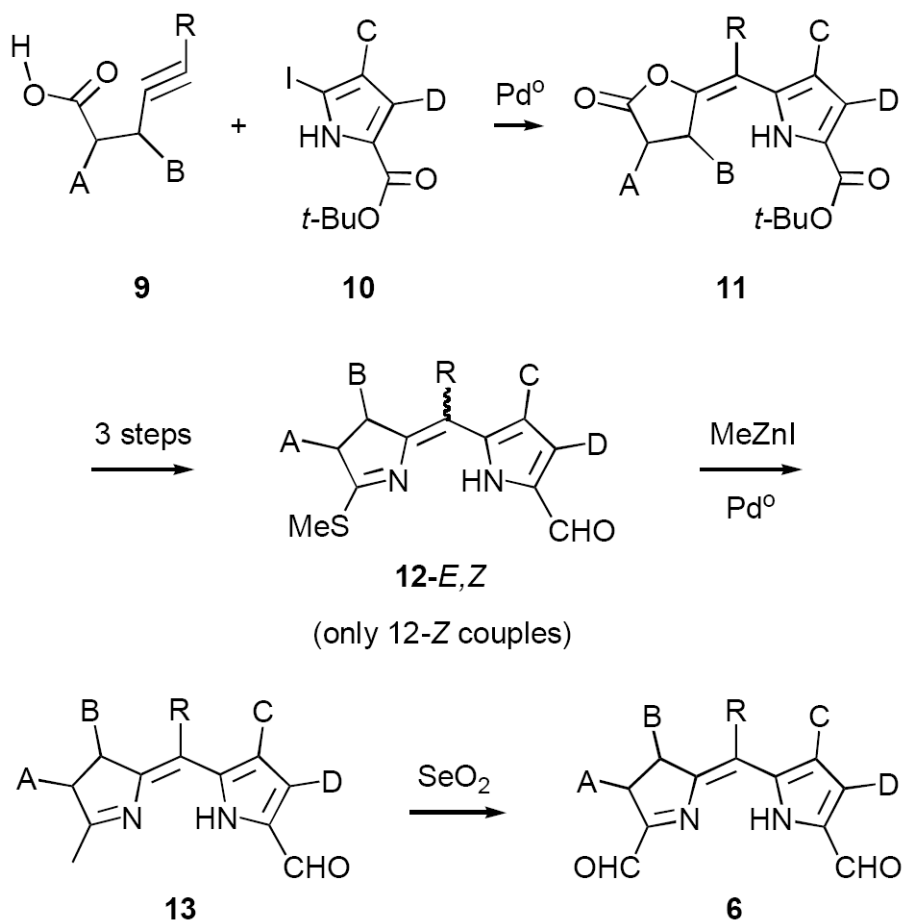
FIGURE 2. Schematic representation of the effect of tether length $-(\text{CH}_2)_n-$ on cellular membrane penetration. The hydrophilic carboxylate groups “anchor” at the aqueous interface.



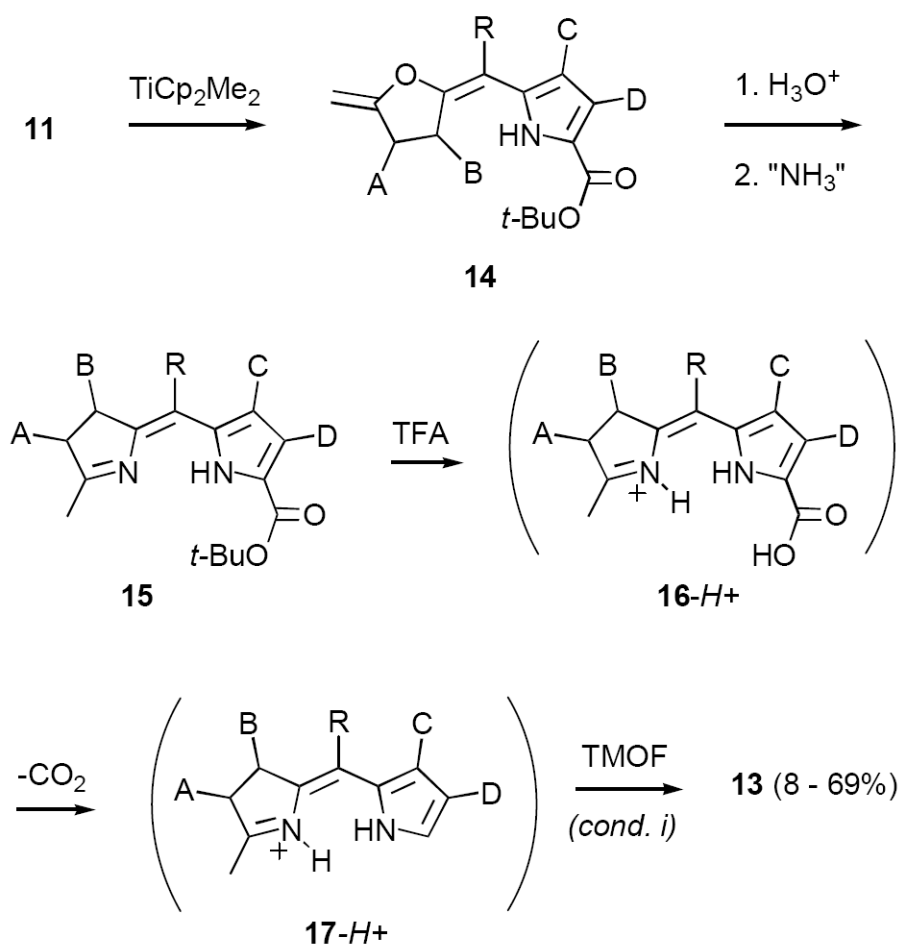
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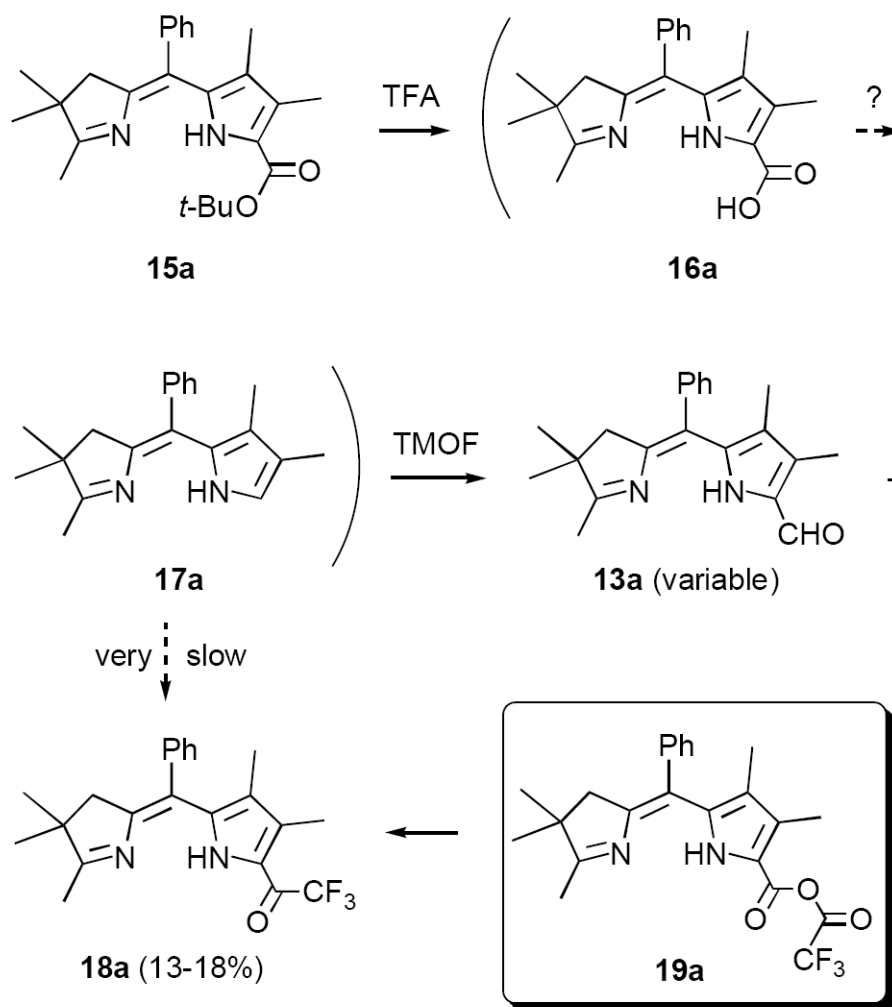
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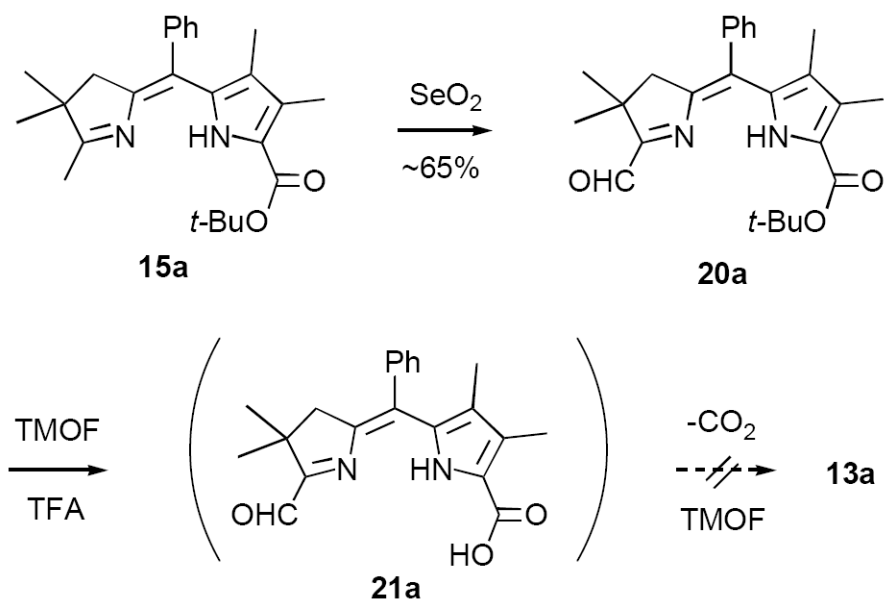
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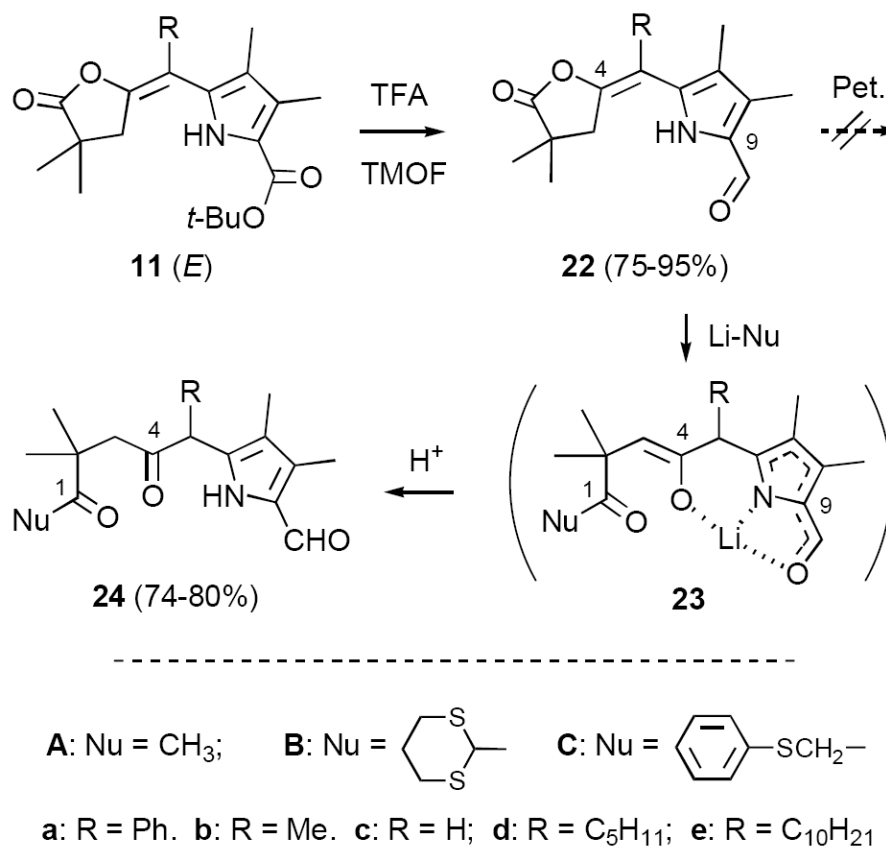
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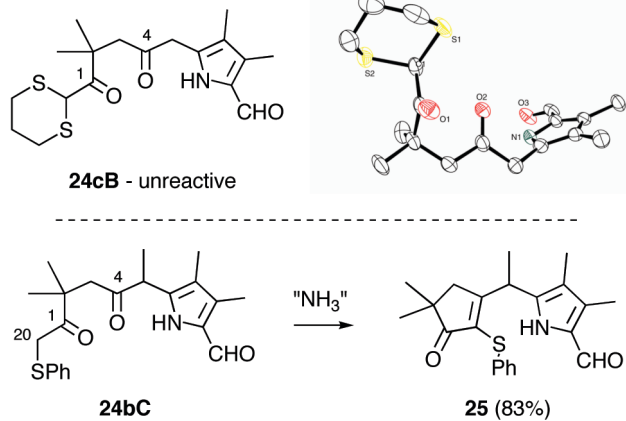
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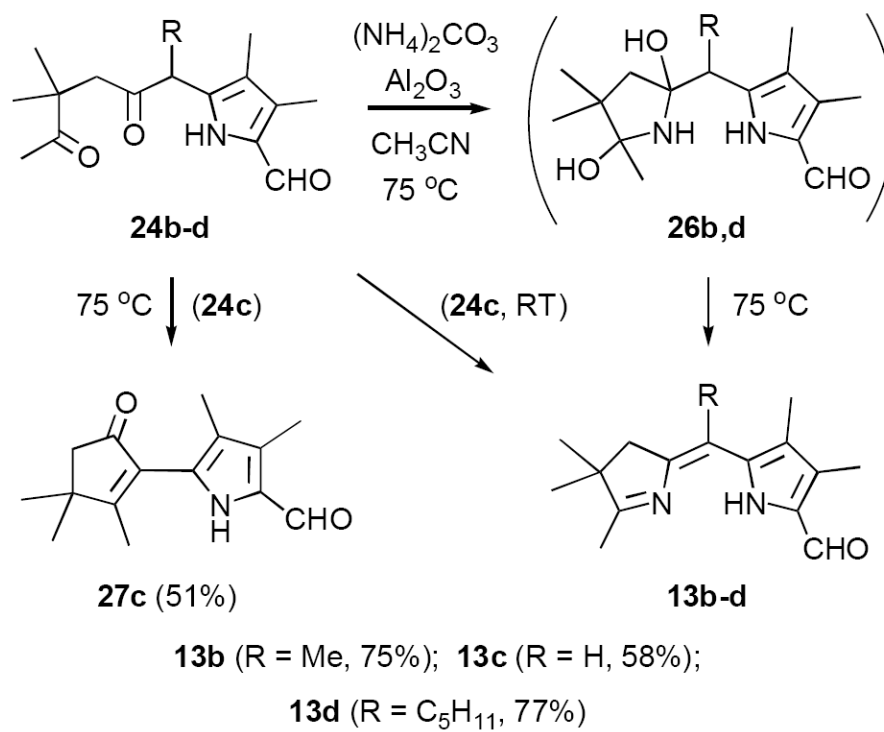
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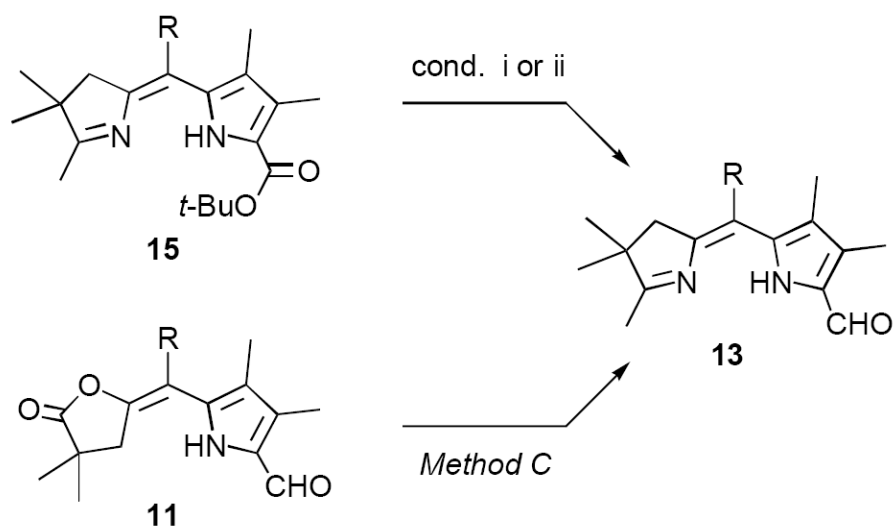
SCHEME 7.



SCHEME 8.



SCHEME 9.



13a (R = Ph, 73%).^b **13b** (R = Me, 75%).^c **13c** (R = H, 71%).^a

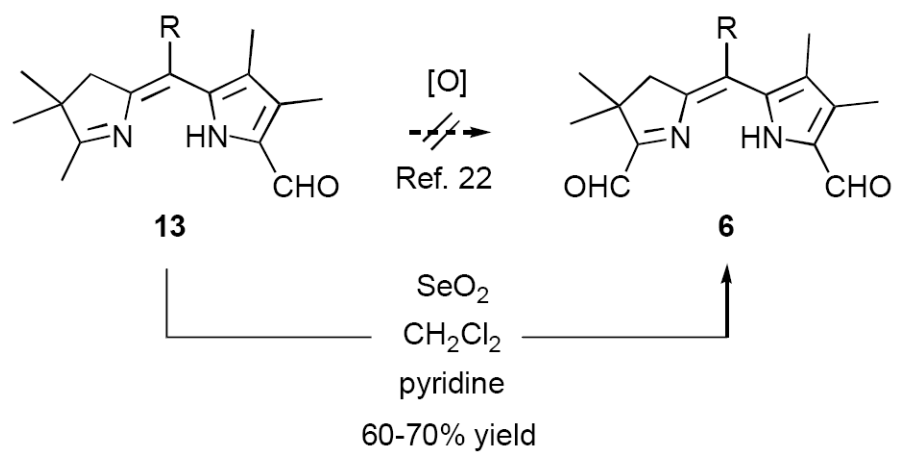
13d (R = C₅H₁₁, 77%).^c **13e** (R = C₁₀H₂₁, 61%).^b

^aconditions i: 1. neat TFA. 2. TMOF, 25 °C.

^bconditions ii: 1. HBr / HOAc. 2. TEOF / CH₂Cl₂. 3. TFA, 0 °C.

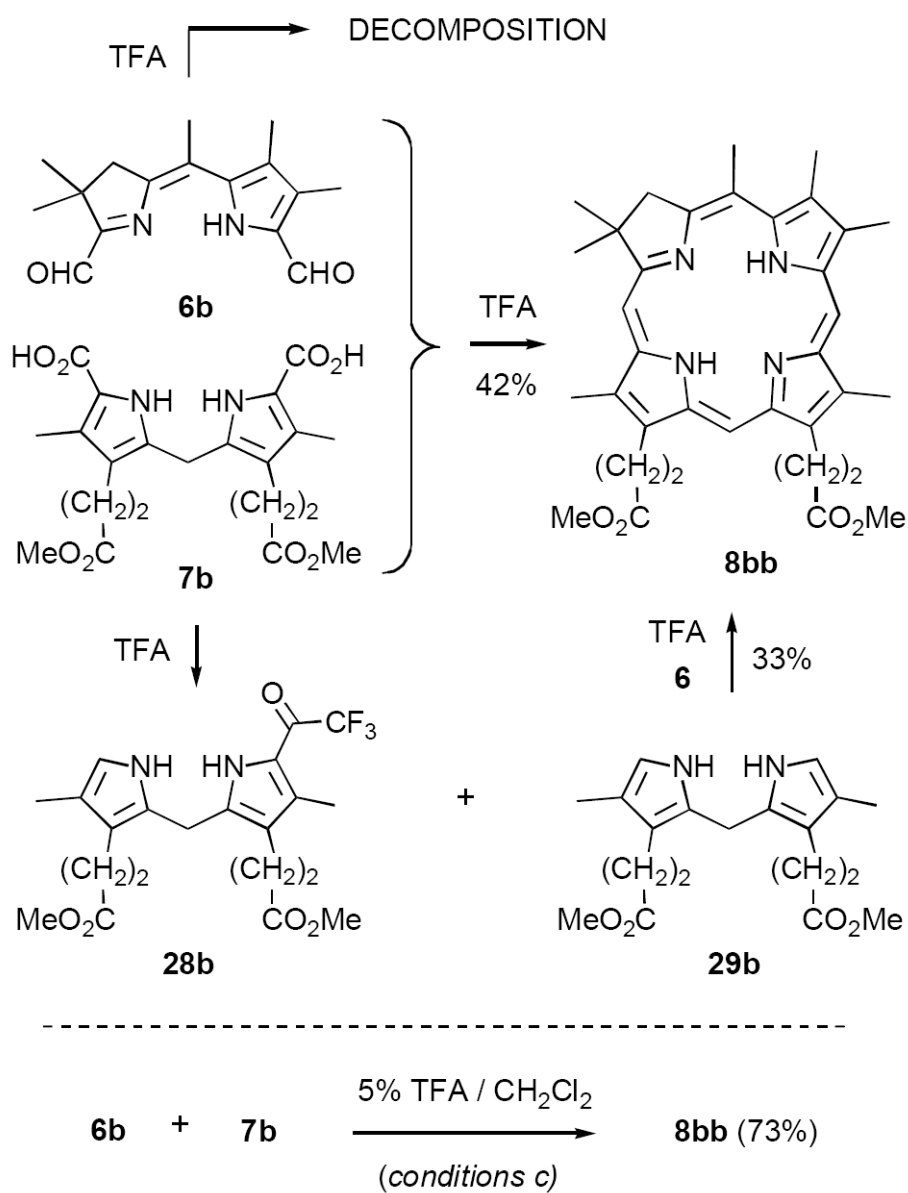
^cMethod C: 1. 2 eq MeLi. 2. (NH₄)₂CO₃ / CH₃CN, 75 °C.

SCHEME 10.



a: R = Ph. b: R = Me. c: R = H; d: R = C₅H₁₁; e: R = C₁₀H₂₁

SCHEME 11.



SCHEME 12.

TABLE 1

15	R	13	Overall yield 13-Z,E
a	Ph		Z (64%) E (9%)
b	Me		25% combined
c	H		<15% combined
d	C ₅ H ₁₁		Z only (57%)
e	C ₁₀ H ₂₁		Z only (61%)

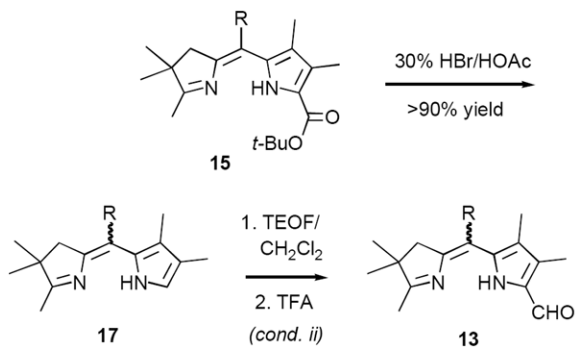
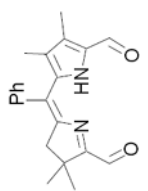
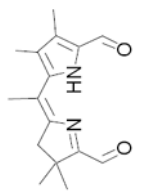
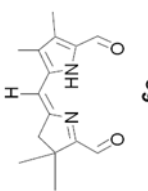
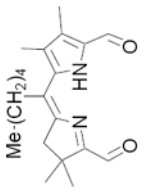
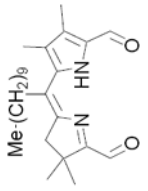
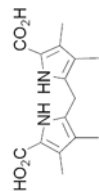
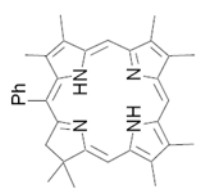
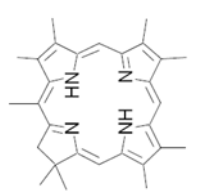
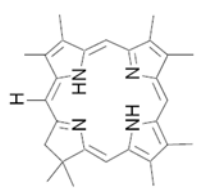
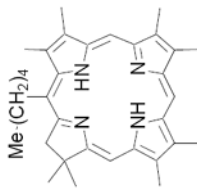
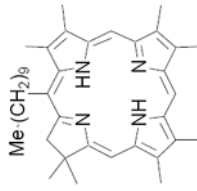
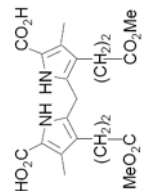
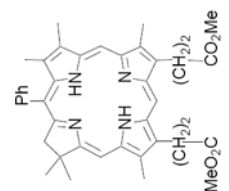
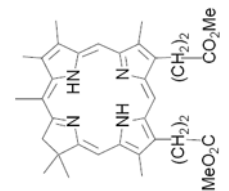
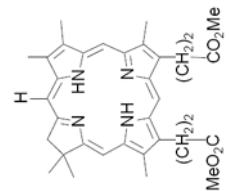
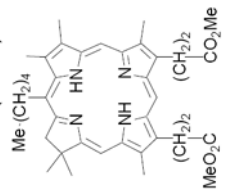
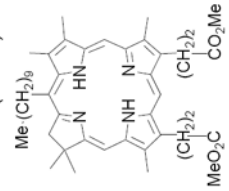
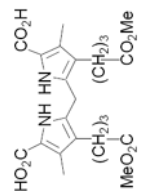
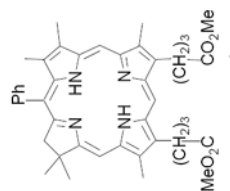
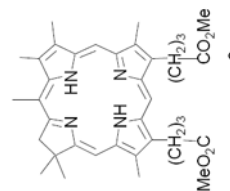
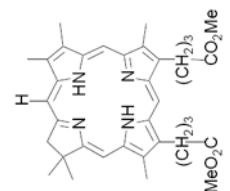
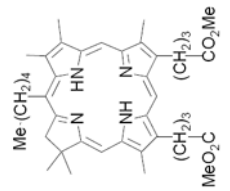
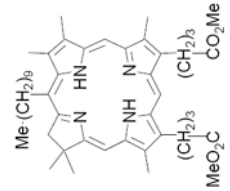
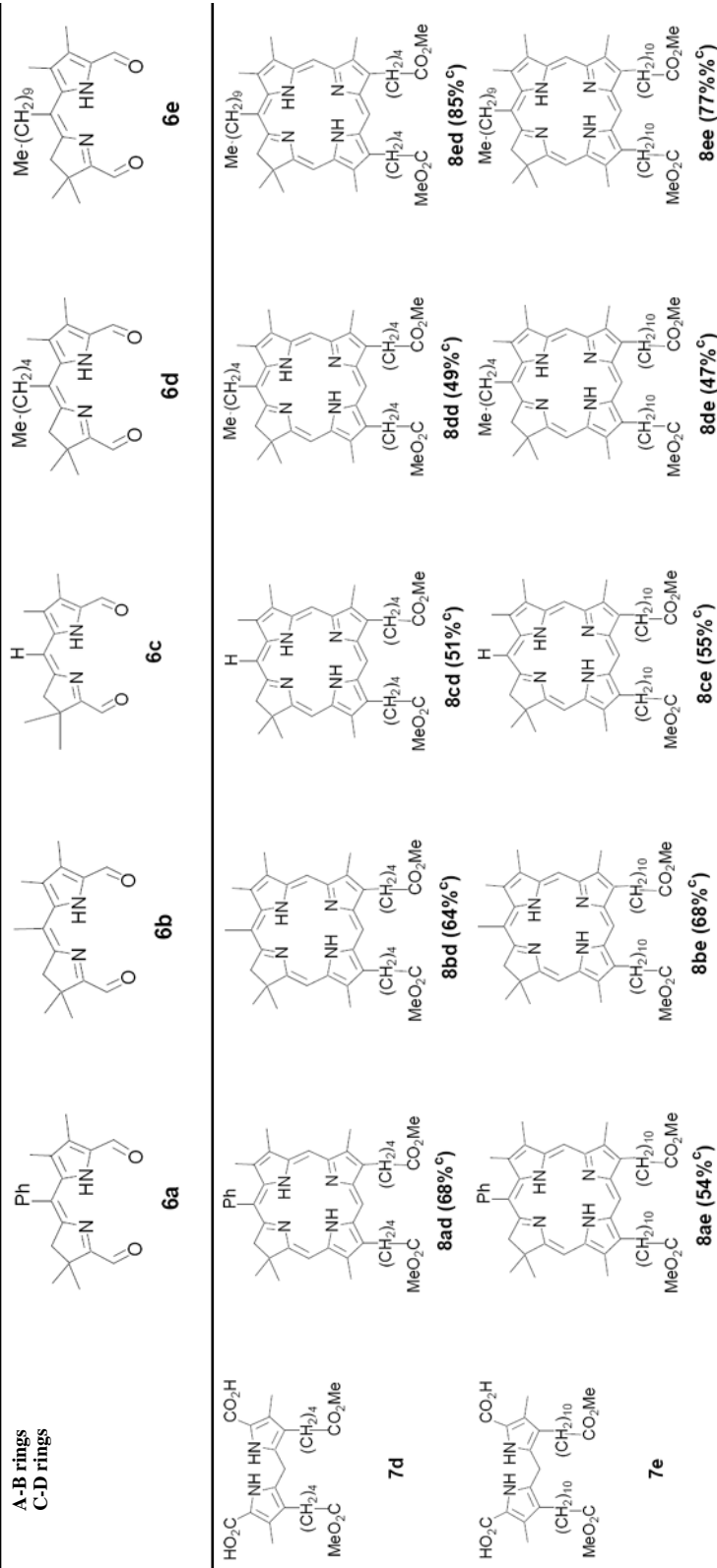


TABLE 2

A-B rings C-D rings					
					
					
					



Conditions: a: neat TFA. b: TsOH/MeOH/CH₂Cl₂. c: 5% TFA in CH₂Cl₂.