Total Synthesis Campaigns Toward Chlorophylls and Related Natural Hydroporphyrins – Diverse Macrocycles, Unrealized Opportunities

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Natural Product Reports
Total Synthesis Campaigns Toward Chlorophylls and Related Natural Hydroporphyrins – Diverse Macrocycles, Unrealized Opportunities

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Quantitative evaluation of reported routes toward bonellin, chlorophyll \( a \), and tolyporphin A suggests heuristics for practical syntheses of native hydroporphyrins.
Abstract

Chlorophylls, bacteriochlorophylls and related hydroporphyrins constitute invaluable natural products but have largely remained outside the scope of viable syntheses. The campaign toward chlorophyll \( a \) by Woodward and coworkers is a deservedly celebrated landmark in organic synthesis yet the route entailed 49 steps, relied on semisynthetic replenishment of advanced intermediates, and then pointed to (but did not implement) uncertain literature procedures for the final transformations. Indeed, the full synthesis at any scale of any (bacterio)chlorophylls – conversion of small-molecule starting materials to the product – has never been accomplished. Herein, the reported syntheses of (±)-bonellin dimethyl ester (0.93 mg) and tolyporphin A \( O,O \)-diacetate (0.38 mg), as well as the never-fully traversed route to chlorophyll \( a \), have been evaluated in a quantitative manner. Bonellin and tolyporphin A are naturally occurring chlorin and bacteriochlorin macrocycles, respectively, that lack the characteristic fifth ring of (bacterio)chlorophylls. A practical assessment is provided by the cumulative reaction mass efficiency (cRME) of the entire synthetic process. The cRME for the route to chlorophyll \( a \) would be \( 4.3 \times 10^{-9} \) (230 kg of all reactants and reagents in total would yield 1.0 mg of chlorophyll \( a \)), whereas that for (±)-bonellin dimethyl ester or tolyporphin A \( O,O \)-diacetate is approximately \( 6.4 \times 10^{-4} \) or \( 3.6 \times 10^{-5} \), respectively. Comparison of the three syntheses reveals insights for hydroporphyrin syntheses. Development of syntheses with cRME >\( 10^{-5} \) (if not \( 10^{-4} \)), as required to obtain 10-mg quantities of hydroporphyrin for diverse physicochemical, biochemical and medicinal chemistry studies, necessitates significant further advances in tetrapyrrole chemistry.
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1 Introduction

Natural products science and synthetic chemistry have been enjoined in an intimate *pas de deux* for nearly two centuries. The isolation of a new substance has prompted synthesis – initially to confirm the structure, and later to create variants thereof for diverse studies. The collaboration constitutes a pillar of modern chemistry that has borne almost immeasurable fruits spanning, for example, medicinal chemistry to our understanding of molecular biodiversity. Yet it is striking if not paradoxical that some of the naturally occurring molecules that once were of great interest have been abandoned, with syntheses incomplete and opportunities unrealized. It is the chlorophylls and related hydroporphyrins to which this charge is directed. In this review, we first outline the key families of hydroporphyrin natural products that contain a chlorin or bacteriochlorin macrocycle, including chlorophylls, bacteriochlorophylls, bonellin, and tolyporphins; broadly overview the chief total syntheses in this domain; and delineate why the synthesis of diverse hydroporphyrin analogues is essential to address far-reaching – and presently fallow – scientific questions concerning these precious compounds and their function in natural systems. Addressing such questions typically requires milligram quantities of target compounds. Hence, we next evaluate three classic syntheses from a quantitative perspective, and propose quantitative evaluation as a critical metric for the success of a synthesis in this domain. Our goal is not to review the chemistry of the individual steps in the syntheses but rather to use the quantitative analysis to glean insights for ultimately gaining the synthetic control required for diverse studies with this repertoire of naturally occurring hydroporphyrins. We finish with a set of synthesis heuristics that emerge from evaluating the three syntheses. Taken together, the objective of this review article is to rekindle interest in the hydroporphyrins as invaluable targets of synthesis.
2 Hydroporphyrin reconnaissance

2.1 Diversity of natural hydroporphyrins

The four types of hydroporphyrins of interest here are displayed in Chart 1. Chlorophyll \(a\) is a preeminent member of the “pigments of life” family\(^1\) and as Nature’s chief light harvester channels the ultimate energy source for most life on Earth.\(^2\) The central chromophore of a chlorophyll is a chlorin (Chart 1), which has one (reduced) pyrrole ring versus the four fully unsaturated rings of a porphyrin. In addition to the simple dihydroporphyrin \(\pi\)-system (with rings A, B, C, D), a natural chlorophyll also contains an additional fifth, “isocyclic” ring (E) substituted with an oxo group. Bacteriochlorophyll \(a\), the chief pigment in anoxygenic bacterial photosynthesis,\(^2,3\) contains two pyrrole rings. While chlorophylls and bacteriochlorophylls are the dominant naturally occurring chlorins and bacteriochlorins, less common chlorins and bacteriochlorins respectively include bonellin, the green coloring matter (and a sex-differentiating hormone) of the sea worm \(Bonellia viridis\),\(^4,5\) and tolyporphins,\(^6-9\) a family of secondary metabolites of unknown \textit{in vivo} function found in a cyanobacterium–microbial consortium.\(^10-12\) Tolyphorin A, the parent member of this family, is photoactive\(^12-14\) \textit{in vitro} and has been reported to inhibit efflux pumps in mammalian cell assays.\(^15,16\)
While chlorophyll \( a \) and bacteriochlorophyll \( a \) are exemplars of the two classes of photosynthetic pigments, other analogues are common in nature: chlorophyll \( b \) occurs along with chlorophyll \( a \) in plants and algae, and various non-oxygenic photosynthetic bacteria rely on bacteriochlorophylls \( b \) and \( a \) together or bacteriochlorophyll \( g \) alone.\(^{2,3,17}\) Other variants of (bacterio)chlorophylls are found in diverse photosynthetic organisms.\(^{2,3,17-19}\) The number of (bacterio)chlorophylls found in Nature easily reaches into the hundreds given variation in the
phytyl unit and peripheral substituents, and products of metal exchange, catabolism, diagenesis and other processes.\textsuperscript{20} Representative members among diverse (bacterio)chlorophylls\textsuperscript{2,3,17-19,21} are shown in Chart 2.

\textbf{Chart 2.} Representative additional naturally occurring (bacterio)chlorophylls.

Tolyporphins to date are found only in one strain, \textit{Tolypothrix nodosa} HT-58-2.\textsuperscript{6,10} A dozen or so tolyporphins have been identified (Chart 3) although stereochemical (and in some cases, isomeric) features have yet to be established.\textsuperscript{7-9} Among the vast literature of glycosylated
natural products, the C-glycosides present in tolyporphins appear to be rare. Tetrapyrrole macrolcycles are almost universally singular products of core metabolism, as required to serve as cofactors in enzymes or photosynthetic proteins. The proposition that tolyporphins are secondary metabolites, an unusual if not unprecedented phenomenon within tetrapyrrole biochemistry, stems from (1) the structural diversity exemplified by variation in the (C-glycoside, acetoxy, and hydroxy) substituents of the pyrroline ring, including promiscuous acetylation of the C-glycoside hydroxy groups, and (2) the presence of a putative biosynthetic gene cluster for tolyporphin biosynthesis as opposed to dispersed organization of genes for biosynthesis of tetrapyrrole end products of core metabolism. Regardless of classification, the biosynthesis and biochemistry of tolyporphins as well as the medicinal chemistry of analogues are almost entirely unexplored.
Sources of (bacterio)chlorins for physicochemical and biological studies include the following: (1) biosynthesis from the first-committed (and universal) precursor δ-aminolevulinic acid;\textsuperscript{23} (2) semisynthesis typically beginning with heme, (bacterio)chlorophylls or derivatives thereof;\textsuperscript{24-36} (3) synthesis from porphyrins, often via hydrogenation or cycloaddition;\textsuperscript{20,37-42} (4) \textit{de novo} synthesis wherein a geminal dimethyl group is located in each pyrroline ring to prevent adventitious oxidation leading to a porphyrin;\textsuperscript{43-48} and, in principle, (5) total synthesis. Total
synthesis efforts toward hydroporphyrins have been incomplete, however, with little scientific impact beyond the field of synthesis itself.

2.2 Rationale for syntheses, albeit incomplete to date

The synthesis program toward chlorophyll $a$ by Woodward and coworkers$^{49-54}$ constitutes a remarkable chapter in the history of organic synthesis, but the heralded commentary$^{55}$ over the years may have fed the misperception that chlorophyll synthesis is a solved problem. The Woodward route entails 49 steps beginning with ethyl acetoacetate and phytol as the chief organic constituents on the path to chlorophyll $a$ (Scheme 1). While brilliant and audacious, the full route has never been traversed from beginning to end. Woodward and coworkers converted ethyl acetoacetate to purpurin 5 dimethyl ester (“ca. 1 mg”)$^{54}$ via chemical synthesis, replenished the stock (75 mg) of purpurin 5 dimethyl ester by degradation of chlorophyll $a$, carried out three subsequent semisynthesis steps to reach chlorin e$_6$ trimethyl ester (3.6 mg), and pointed to “well-trodden paths”$^{49}$ for the conversion of chlorin e$_6$ trimethyl ester and phytol to chlorophyll $a$. Subsequent work has addressed these latter steps,$^{56}$ and methods have been developed for conversion of chlorophyll $a$ to chlorophyll $b$.$^{57,58}$ Note that the 49-step synthesis did not include the synthesis of phytol; an independent synthesis reported at that time required 6 steps from (+)-citronellol or 7 steps from (+)-(R)-methyl hydrogen β-methylglutarate and 4-methylpentanoic acid.$^{59,60}$ The phytol synthesis was designed to elucidate stereochemistry and also was a relay synthesis, relying on ozonolysis of natural phytol to afford an advanced intermediate (the C$_{18}$ ketone), hence the complete chemical synthesis of phytol also was not fully traversed (but has since been fleshed out$^{61}$). Phytol represents 1/3 of the mass of chlorophyll,$^{46}$ and while not part of the $\pi$-chromophore, plays a key organizational role in photosynthetic systems.
Scheme 1. Outline of Woodward synthesis campaign toward chlorophyll $a$.

The synthesis of (±)-bonellin dimethyl ester has been reported by two groups,$^{62-65}$ and tolyporphin A $O,O$-diacetate$^{66}$ has been reported on one occasion (an earlier synthesis$^{67}$ obtained the $O,O$-diacetate of a stereoisomer of the natural product$^{68}$). Synthetic efforts toward naturally occurring or naturally derived hydroporphyrins are described in a comprehensive (but somewhat older) review by Montforts and coworkers.$^{21}$ The synthesis efforts toward chlorophyll $a$, bonellin, tolyporphin A and other hydroporphyrins unequivocally established structures and constitute towering achievements in organic chemistry, but have not proved to be workhorses for
generation of analogues or scaffolds in physical, chemical, and/or biological studies. The chlorophyll \textit{a} synthesis campaign, for example, was enormously fecund in tetrapyrrole chemistry and in broadly reimagining scientific possibilities for synthesis, but in fact has had no impact in plant sciences or photosynthesis, the \textit{raison d’être} of chlorophyll.\textsuperscript{46} More broadly, to our knowledge, no small-molecule starting material (e.g., ethyl acetoacetate or a monopyrrole) has ever been converted by chemical synthesis to a chlorophyll or a bacteriochlorophyll of any type. Indeed, the foundational support that natural products synthesis programs typically afford in the creation of novel variants of the natural structures has been strikingly absent from the hydroporphyrin field, constituting a significant intellectual and technical deficit.

The rationale for the total synthesis of (bacterio)chlorophylls and hydroporphyrin analogues includes the following.

1. Employ isotopologues bearing \textsuperscript{2}H, \textsuperscript{13}C and/or \textsuperscript{15}N at designated sites in the macrocycle skeleton to delineate the vibrational normal mode analysis\textsuperscript{69} and to probe vibronic contributions to excited-state energy transfer\textsuperscript{70,71} (i.e., quantum coherence).

2. Use structural variants, including phyllobilins and macrocycles, for functional analysis in reconstituted photosynthetic systems and examination of fundamental properties, such as the importance of auxochromes and \textit{trans}-dialkyl pyrroline substituents.

3. Obtain synthetic analogues of bonellin, tolyporphins, and (bacterio)chlorophylls for use in pull-down assays to identify binding proteins and/or biosynthetic enzymes, and to examine biochemical properties, microbial interactions, ecological fate, and nutritional features. The same approach is invaluable to explore catabolism – some $10^9$ tons of chlorophyll is broken down globally each year,\textsuperscript{72} and only recently has the nature and fate of such catabolites begun to be probed,\textsuperscript{73} essentially nothing is known about bacteriochlorophyll catabolism and products therefrom.
(4) Challenge the creation of new synthetic methodology including at least the following: preparation and manipulation of pyrroles and pyrrolines, the latter enantiopure with trans-dialkyl or cis-dialkyl substituent patterns; construction of dipyrromethanes, dipyrrins, bilins and phyllobilins; macrocyclizations yielding hydroporphyrins with diverse stabilization motifs; and site-specific derivatization of hydroporphyrins.

In the next three sections, we analyze the reported routes to chlorophyll a, (±)-bonellin dimethyl ester, and tolyporphin A O,O-diaceate from a quantitative perspective. Our focus on these macrocycles begins with the centrality of (bacterio)chlorophylls in photosynthesis, and extends to the two non-photosynthetic molecules for point of contrast: the chlorin bonellin (in racemic form and as the dimethyl ester) is simpler architecturally than chlorophyll, and tolyporphin A (as the O,O-diaceate) is the only naturally occurring bacteriochlorin for which a total synthesis has been reported. Both bonellin and tolyporphin A lack the characteristic fifth ring of (bacterio)chlorophylls.

3 Woodward’s campaign toward chlorophyll a

3.1 Reaction steps

The chlorophyll a synthesis program by Woodward and coworkers began in 1956 and was first reported in 1960.\textsuperscript{49} The ingenuity of the synthesis has been duly lauded on numerous occasions,\textsuperscript{20,46,55,74-78} including discussion of the monumental nature of the undertaking without benefit of the powerful methods of the present era.\textsuperscript{46} Here, the thrust is a dispassionate quantitative analysis, which is made possible by the comprehensive report\textsuperscript{54} spearheaded by Bonnett,\textsuperscript{53} a generation following the synthesis and a decade following the passing of Woodward.\textsuperscript{79} The quantitative analysis reported here would not be possible without the expanse, detail, and candor of the full report\textsuperscript{54} versus the 1960 communication.\textsuperscript{49} An expanded flowchart
for the chlorophyll \(a\) route is shown in Scheme 2. The synthesis was divided into four stages: (I) preparation of four pyrrole precursors that ultimately give rise to the four pyrrolic rings (A, B, C, D) of the macrocycle (steps 1–25); (II) synthesis and elaboration of the AD and BC halves for macrocycle formation (steps 26–32, 7 steps); (III) macrocycle formation (steps 33–35, 3 steps); and (IV) subsequent manipulation to finalize the peripheral substituents, convert the porphyrin to the chlorin, construct the isocyclic ring E, chelate Mg(II), and attach the phytol unit (steps 36–49, 14 steps). Were the phytol synthesis\(^{59,60}\) of that era included, the total synthesis would entail 56 steps. The compound numbers and steps are those employed in the original Woodward work as delineated in the full report.\(^{54}\)
Scheme 2. Flowchart showing the four stages of Woodward’s chlorophyll a route.

All four pyrrolic rings (A, B, C, D) were prepared from Knorr’s pyrrole, a stable pyrrole with potential to be manipulated selectively at every site. Thus, extensive chemistry was done to tailor all the substituents except the 3-methyl group; the latter gave rise to the 2,7,12,18-
tetramethyl substituents of the target macrocycle. Knorr’s pyrrole could be easily prepared from simple commercial materials (ethyl acetoacetate, NaNO$_2$, acetic acid and zinc powder) at reasonably large scale. Indeed, several kilograms of Knorr’s pyrrole was likely prepared and consumed during the study.$^{54}$ Structures 1-25 and yields for each step (which generally are quite high, 45–98%) are shown in Scheme 3.

The synthesis of the ring A precursor (10 steps from Knorr’s pyrrole) entailed manipulation of the β-substituents and freeing up the α-positions (Scheme 3, top panel). The strategy to introduce the 3-vinyl group of chlorophyll a relied on installation of a 2-aminoethyl unit in the ring A precursor. As a result, 8 out of 10 steps for ring A preparation entailed replacement of the 3-CO$_2$Et group with the 3-(2-aminoethyl) group, while conversion of the 5-methyl to a removable methoxycarbonyl group and removal of the α-substituents each required one step. The overall yield from Knorr’s pyrrole (1) to 11 was 12%. Note that where a yield range for a step was reported, the median has been taken for calculation.

The synthesis of the ring B precursor consisted of 5 steps starting from pyrrole 3, including 2 steps for installation of an ethyl group and 3 steps for tailoring an α-substituent for condensation (Scheme 3, second panel). The yield of ring B precursor 16 was 47% from pyrrole 3, and 36% from Knorr’s pyrrole (1). The preparation of ring C precursor 20 (Scheme 3, third panel) entailed straightforward removal of both α-substituents from Knorr’s pyrrole (1) in 39% yield.

The generation of ring D precursor pyrrole 25 entailed a 5-step procedure from pyrrole 4, including 2 steps for the elaboration of a β-formyl to a propionic acid group, and 3 steps for installation of a 2-formyl group for condensation (Scheme 3, bottom panel). The yield of pyrrole 25 was 20% from pyrrole 4, and 15% from Knorr’s pyrrole (1). The four precursor pyrroles (11, 16, 20, 25) provided the requisite peripheral substituents of the final synthetic target chlorin e$_6$
trimethyl ester (46) except for the vinyl group (as a latent 2-aminoethyl entity) at the 3-position, and the 13-substituent was ethoxycarbonyl (versus the requisite methoxycarbonyl).

Scheme 3. Preparation of precursors to rings A–D.
Given the absence of a route to an unsymmetrically substituted chlorin or porphyrin macrocycle substituted with an electron-withdrawing group (-CO₂Me group) at ring C, an electron-rich dipyrromethane (AD half, also termed the “Western-half”) bearing two open α-pyrrole sites was condensed with an electron-poor dipyrromethane (BC half, or “Eastern-half”) bearing α-carbonyl and α-thioformyl substituents. The AD half 26 was prepared from pyrroles 11 and 25 in 56% yield as a dipyrrin hydrochloride (Scheme 4, top panel). The BC half 31, wherein a 4-methoxy-4-oxobutanoyl unit at one α-position is destined to serve as the macrocycle 15-substituent, was prepared from pyrroles 16 and 20 in 30% yield as a dipyrromethane (Scheme 4, middle panel). Porphyrin 35 was prepared from dipyrrin 26 (via dipyrromethane 32) and dipyrromethane 31 in 4 steps (50% yield) without isolation of any intermediates (Scheme 4, bottom panel).
Scheme 4. Preparation of AD (32) and BC (31) halves for conversion to a porphyrin (35).

The porphyrin–chlorin conversion, including construction of the trans-dialkyl configuration in ring D, was achieved by leveraging the “peripheral overcrowding effect”.\textsuperscript{49} In so doing, a reversible porphyrin–chlorin interconversion was discovered (between porphyrin 36...
and purpurin 37). Eventually, chlorin 41 was prepared from porphyrin 35 in 7 steps (Scheme 5). The yield for steps 36–41 was 2.6%. Although most reactions in the process to this point exhibited modest to good yields, the stereoisomer resolution (step 42) proceeded in 4% yield. Consequently, only “ca. 1 mg” of chlorin 43 was isolated as the final product of the chemical synthesis.\textsuperscript{54} After that, 75 mg of chlorin 43 derived by degradation of chlorophyll \textit{a} (via established procedures\textsuperscript{80}) was added to replenish the stock.

Scheme 5. Macrocycle manipulation completing the chemical synthesis.

Subsequent steps 44–46 transformed chlorin 43 to chlorin \textit{e}_6 trimethyl ester (46), but two of the steps exhibited quite low yields, affording 2.4% yield for the three-step process (Scheme
Despite the relay synthesis, 3.6 mg of chlorin e₆ trimethyl ester (46) was isolated as the final product of the synthesis/semisynthesis undertaking.

The “well-trodden” transformations (steps 47–49) to finish the synthesis would have entailed cyclization to form ring E, attachment of the phytol tail, and chelation of magnesium (Scheme 6). As no experimental detail was described for the original procedures, we turned to subsequent cyclizations for which yields of 97% and 66% were reported; here we used the 97% value for the calculations. We also employed the yields for phytol attachment and Mg(II) insertion reported subsequently by Smith and Lewis. The overall yield for these three essential transformations was estimated to be 42%.

Scheme 6. Semisynthesis of chlorin e₆ trimethyl ester (46) and culminating “well-trodden paths” towards chlorophyll a (49).

3.2 Estimating the requisite quantity of starting materials

For diverse studies of hydroporphyrins, quantities of 1–10 mg are typically required. Here, we sought to estimate the total quantity of starting materials and reactants required to implement and
fully traverse the reported synthesis. The amounts are not immediately obvious from even the comprehensive experimental section\textsuperscript{54} candidly assembled by Bonnett\textsuperscript{53} because (1) some procedures were repeated multiple times; (2) some products along the way were diverted, as is typical in synthesis; (3) one relay step was employed; and (4) some procedures were not implemented but were pointed to in the literature. In other words, one cannot merely look at the reported procedure for the first step of the synthesis (Knorr’s pyrrole, 1) and gauge the requisite scale to prepare chlorophyll \(a\) in any given amount.

The quantity of Knorr’s pyrrole consumed to produce the \(~1\) mg of chlorin 43 was not reported, but the minimum quantity can be estimated on the basis of the analysis above. To obtain \(~1\) mg (taken hereafter to be 1.00 mg) of chlorin 43 as the final synthetic product would require at least 0.494 mol (118 g) of Knorr’s pyrrole, corresponding to 1.73 mol (225 g) of ethyl acetoacetate. Given that the batch of Knorr’s pyrrole was split four ways to prepare the four pyrrole rings, an overall yield for the synthesis cannot be calculated. Regardless, the efficiency factor in terms of mass (1.00 mg/225 g) would be \(4.44 \times 10^6\) for conversion of ethyl acetoacetate to chlorin 43.

The above numbers are not unacceptable for natural products total synthesis. However, to repeat the full synthesis towards chlorin \(e_6\) trimethyl ester (46) but without any semisynthetic material replenishment, each 1 mg of chlorin \(e_6\) trimethyl ester (46) would require 67.6 mol (8.75 kg) of ethyl acetoacetate (19.3 mol = 4.59 kg of the common precursor Knorr’s pyrrole). The 3.6 mg of chlorin \(e_6\) trimethyl ester (46) obtained as the final product would require 243 mol (31.5 kg) of ethyl acetoacetate. The efficiency factor in terms of mass is \(1.14 \times 10^7\). If the final “well-trodden paths” were further included, 1 mg of the target chlorophyll \(a\) would require 113 mol (14.7 kg) of ethyl acetoacetate, for an efficiency factor in terms of mass of \(6.80 \times 10^8\).
(Note that the displayed yield of 26% for step 46 is actually 36% according to the experimental section;\textsuperscript{54} we have employed the latter value in the calculations herein.)

To better understand the origin of the low efficiency of the chlorophyll $a$ synthesis, the material diminution for each individual step is illustrated in Figure 1. The figure – inspired by Minard’s graph of Napoleon’s campaign to and from Moscow\textsuperscript{85} – contains six data modalities: (1) quantity of material in mols/step (y-axis), (2) step # (x-axis), (3) yield/step (bar labels), (4) ring or dipyrrin identity (bar color), (5) synthesis stage (dashed enclosures) and (6) reliance on other materials or paths (arrows). The path uses step numbers and yields from the full report,\textsuperscript{53,54} begins with the 1.73 mol of ethyl acetoacetate (EtAA) implied (vide supra), affords the stated \textasciitilde1 mg of purpurin 5 dimethyl ester (43) obtained via the chemical synthesis as well as the 3.6 mg of chlorin $e_6$ trimethyl ester (46) obtained from the follow-on semisynthesis, and lists the yields and amounts upon conversion of 46 to 49 (chlorophyll $a$) that we have estimated from post-1960 procedures. The pyrrole precursor syntheses section (stage I) entailed 25 steps, constituting half of the synthesis. For the first half of the synthesis, the individual steps generally exhibited 45\% to 98\% yield with acceptable overall efficiency, whereas some of the following steps suffered from quite low yields. The lowest yield (4\%) was encountered in step 42 – resolution of the ring-D stereoisomers.
Figure 1. Quantitative analysis of Woodward’s chlorophyll α total synthesis campaign. Note the log scale for the y-axis.
Cumulative reaction mass efficiency

The evaluation of a synthesis by considering the quantity of the most abundant carbon-containing material provides one quantitative perspective, in this case the scale required for implementation of the first step to make Knorr’s pyrrole from ethyl acetoacetate. Several approaches have been developed to assess the total required materials for a process. An established approach in green chemistry concerns the “reaction mass efficiency” or RME, which is the ratio of the product mass versus the sum of the mass of various materials for a given chemical reaction. Three common RME definitions have been put forth depending on how expansive the “various materials” are assessed: (1) the kernel RME, which is the product of the reaction yield and the atom economy; (2) Curzon’s RME, which takes into consideration actual masses of reactants and reagents that contribute to the mass of the product (in actual quantities employed, even beyond direct stoichiometric quantities) and sometimes additional entities required to balance a reaction (e.g., base in an acid-generating reaction); and (3) the generalized RME (gRME) that takes into consideration the mass of all chemical entities employed in the reaction, including organic reactants, reagents, catalysts, ligands, etc., solvents and work-up/purification material (e.g., all silica gel, solvents for chromatography and recrystallization). The concept of extending RME from a single reaction process to a serial process involving many reaction steps, termed as overall or cumulative reaction mass efficiency (cRME), is exceptionally attractive for our purposes compared with other methods (e.g., atom economy) for evaluating synthetic routes.

We calculated a Curzon type of cRME because the amount of solvents, catalysts and work-up/purification materials are unclear or not reported for the three hydroporphyrin syntheses evaluated here. Only the quantities of starting materials (i.e., reactants) and those reagents that contribute to the product are considered, in the amounts specified regardless if in excess beyond
the stoichiometric requirement. However, a material that serves both as solvent and a reactant would be considered in the sum of the mass; for example, the DMF in a Vilsmeier formylation or the water in a hydrolysis process. In summary, we use the cRME term to refer to all materials (reactants and reagents in their actual quantity but not solvents or purification materials). To gauge the sensitivity of the cRME calculation to selected cases where the solvent serves as reagent and hence is included, we employed a modified term, cRME′, where such a reagent is employed in the calculation at a stoichiometric level.

This analysis is compatible with a mixed process of linear and convergent approaches, as is the case in the chlorophyll a route, because such processes require the product of a given step being used in full as the reactant for the immediate subsequent step (as defined in the calculation of cRME). No accounting is made for any diversion of an intermediate – such as setting aside a portion of the product for characterization, studies of reaction optimization, or security for reaction repetition in case subsequent reactions fail. Such analysis establishes the minimum requirement for materials. In cases where the reported scale of step $n$ is insufficient for carrying out step $n + 1$, the implication is that step $n$ must have been carried out more than once. For our calculation of cRME, step $n$ is rescaled to match the amount required for step $n + 1$ (see Supporting Information for an illustrative example).

In this manner, the cRME for steps 1–43, 1–46, and 1–49 of the chlorophyll a route have been calculated on the basis of the published yields and experimental procedures with linear scaling to obtain 1 mg of chlorophyll a by chemical synthesis alone. The results are shown in Table 1. The masses of reactants and reagents were not reported for steps 2, 13, 17, 19, and 21; hence we calculated the amounts on the basis of cited procedures. The amounts of O$_2$ (steps 36 and 39), excess CH$_2$N$_2$ (steps 24, 31, and 40) and H$_2$ (step 11) were not reported but here were estimated stoichiometrically. The overall cRME for the chlorophyll a synthesis (steps 1–49)
is estimated to be $\sim 4.3 \times 10^9$. In other words, the synthesis of 1 mg of chlorophyll $a$ would have required at least 230 kg of reactants and reagents. Upon comparing the quantities required for steps 1–43 versus 1–46, one can see why Woodward and coworkers discontinued *de novo* synthesis upon completing step 43 and turned thereafter to a relay approach.

**Table 1.** cRME for the chlorophyll $a$ synthesis

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</table>

One observation warrants comment. The precipitous decline in yields upon macrocycle manipulation (stage IV, Scheme 2) caused the scale of such reactions to be profoundly small versus those at earlier stages of the synthesis. Accordingly, the additional materials at these later steps have little impact on the magnitude of the cRME, but the low yields significantly increase the required scale of the early reactions. Overall, the total mass of all materials is about 17.3 times that of the required amount of ethyl acetoacetate (Figure 1). We emphasize that this cRME represents a lower bound on required materials, taking into account only the reactants and not the reaction solvent and catalysts and all of the materials (solvents, chromatographic media) employed during purification. To examine whether such a low cRME value is inevitable in hydroporphyrin syntheses, we now turn to the syntheses aimed toward two other native hydroporphyrins, bonellin and tolyporphin A.

4 **Battersby’s synthesis of (±)-bonellin dimethyl ester**
Bonellin among members of the natural hydroporphyrin family has a relatively simple structure (Scheme 7, R = H): methyl or propionate substituents, only one stereocenter, and no metal chelate. Battersby and coworkers demonstrated the first total synthesis of (±)-bonellin dimethyl ester (Scheme 7, R = Me), obtaining 0.93 mg via a photochemical “2 + 2” approach in 1983. Montforts and coworkers later reported a “3 + 1” route to (±)-bonellin dimethyl ester that made use of a novel ring D precursor employed in the total synthesis of cobalamin (because ring D of bonellin is structurally and stereochemically identical to ring C of cobalamin). The route attempted an enantiopure synthesis wherein (+)-camphor was the starting material for generating the chiral ring D, but epimerization upon sulfide contraction to generate a very late-stage intermediate (a tripyrrin containing rings B–D) resulted in racemic bonellin dimethyl ester (9.7 mg). While both routes have merit, here we have subjected Battersby’s (deliberately racemic) route to quantitative analysis.

Scheme 7. Precursors in Battersby’s synthesis of (±)-bonellin dimethyl ester.
As shown in Scheme 7, the precursors of rings A–D are from four different precursors (pyrroles B-1–B-3 and Michael acceptor B-4) in this synthesis. The compound numbers used here do not correspond to those in the original report.\(^{62}\) The four precursors can be further obtained from various simpler commercial materials (B-17–B-21). The ready availability of precursors reflects considerable synthetic and commercial development over the years for the preparation of small molecules, especially pyrroles B-18 and B-19.

The synthetic route is shown in Scheme 8. The yields are taken from the detailed experimental procedure reported in 1988.\(^{64}\) The synthesis entails the preparation of AD (4 steps) and BC (6 steps) halves, macrocycle formation (1 step) and manipulation of one side chain of the macrocycle (1 step). Compared with the synthesis of chlorophyll \(\alpha\), this route is much shorter and does not involve extensive conversions after the macrocycle has been formed. The yields are generally modest to good, except for the step of macrocycle formation, which proceeds in 20% yield due to the low conversion of starting material (97% yield if recovered material is taken into account). The amount of (±)-bonellin dimethyl ester\(^{64}\) obtained was small (0.93 mg) yet sufficed to establish structure and provide the first \textit{de novo} route to a gem-dimethyl substituted chlorin.
Quantitative analysis shows that to obtain 1.00 mg of (±)-bonellin dimethyl ester would require the following quantities of starting materials: pyrrole B-1, 5.87 mg; pyrrole B-2, 21.2 mg; pyrrole B-3, 10.9 mg; and Michael acceptor B-4, 7.36 mg. The cRME for the synthesis (step 1–13) is $6.71 \times 10^{-4}$. If earlier commercial materials are considered (Scheme 7), obtaining 1.00 mg of (±)-bonellin dimethyl ester would require the following precursors: B-17, 34.5 mg; pyrrole
B-18, 24.1 mg;\textsuperscript{64} pyrrole B-19, 12.6 mg;\textsuperscript{94} B-20, 57.1 mg; and B-21, 7.60 mg.\textsuperscript{95} The cRME for the entire process is $6.36 \times 10^{-4}$. It may be regarded as unusual that B-18 and B-19, both of which are pyrroles, are available commercially. B-19 can be prepared from a Knorr synthesis in 32\% yield,\textsuperscript{96} whereas B-18 can be similarly obtained\textsuperscript{97} in quantitative yield followed by a cleavage of benzyl ester group.\textsuperscript{98} Taking these pyrrole-forming transformations into account gives a resulting cRME of $5.6 \times 10^{-4}$.

The relatively small quantities of starting materials reflect high yields in many of the reactions and a reasonably concise synthesis. Even with a substantial yield loss upon cleavage of the esters to give native but racemic bonellin, a sufficient amount of (±)-bonellin or analogues for further studies appears accessible with this synthetic route. Additional facets of the synthesis require consideration beyond the quantitative analysis here; for example, Battersby and coworkers actually employed multigram-quantities of starting materials (2.1 g of B-1, 15 g of B-3). Why then was < 1 mg of (±)-bonellin dimethyl ester obtained?

Steps 4 and 10 were carried out with only 1/10\textsuperscript{th} and 1/8\textsuperscript{th}, respectively, of the B-7 or B-13 obtained, and macrocycle formation (step 11) was carried out with ~1/10\textsuperscript{th} of the B-8 and B-14 obtained (9 and 6.5 mg, respectively). The rationale for the decisions to proceed with diminished quantities of material is unclear – perhaps the subsequent reactions could be poorly scalable. Indeed, the photochemical ring closure (step 12) at least in that era was likely not amenable to implementation with quantities of more than a few mg. The upshot of these caveats is that the calculated masses of the starting materials and the cRME values provide perspective but alone do not imply scalability. It also warrants comment that the cRME values can be altered considerably when a particular reagent is used in very large excess. For example, steps 9 and 13 employ a reagent as the solvent (DMF and MeOH, respectively). In the case that the calculation is done with stoichiometric quantities of each, the cRME’ value would be $2.4 \times 10^{-3}$. Regardless,
quantitative analysis suggests that (±)-bonellin and analogues should be readily accessible at the 10-mg scale assuming reasonable scalability of the photochemical ring closure. A fundamentally distinct approach to formation of the propionate-substituted pyrroline ring would be required to achieve an enantiopure or enantioselective route to the native bonellin.

5 Kishi’s synthesis of tolyporphin A O,O-diacetate

Tolyporphin A (T-2a, Scheme 9) is the parent member of a family7-9 of novel unsymmetrical dioxobacteriochlorins. The total synthesis of tolyporphin A O,O-diacetate (T-2b, 0.38 mg) was reported by Wang and Kishi in 199966 after several years of pioneering work by Minehan and Kishi67,99,100 alone and in conjunction with the original discovery team,68 thereby establishing the stereochemistry of the isolated natural product tolyporphin A.

The core building blocks to construct the tolyporphin macrocycle are three monocyclic precursors T-4, T-5, and T-12 (used twice). T-4 and T-5 give rise to pyrrole rings B and D whereas T-12 gives the two pyrroline rings A and D. The preparation of these three monocyclic precursors is shown in Scheme 10 (upper panels). The synthesis of precursor T-4 (steps 1, 2) or T-5 (steps 3, 4) consisted of two steps from the commercial \( \gamma \)-butyrolactone or \( \alpha \)-methyl-\( \gamma \)-butyrolactone, respectively. Precursor T-11 was prepared in a 4-step procedure (steps 5–8) starting from the C-glycoside precursor pre-T-6a and the dihydrofuran T-9. The compound numbers used here correspond to those in the original report (except for pre-T-6a, which is referred to as “methyl \( \alpha \)-glycoside” in the original paper) and our generic application of the “T” prefix. Conversion of T-11 to T-12 entailed a 7-step process that proceeded in 47% yield. The enantiopure T-12 derived ultimately from the chiral species pre-T-6a and the dihydrofuran T-9; the former was obtained from methyl \( \alpha \)-D-galactopyranoside in a 6-step process, whereas the latter was derived from L-(S)-glutamic acid in a 4-step process. The preparation of the two precursors is shown in Scheme 10 (lower panels).
Scheme 10. Synthesis of three key building blocks (T-4, T-5, T-12; upper panels) and two precursors (pre-T-6a, T-9; lower panels) for tolyporphin A O,O-diacetate.
With the ring precursors in hand, macrocycle construction was completed following an established protocol. First, the Eschenmoser sulfide contraction method was extended to the preparation of the AB half (T-15) and CD half (T-16) (Scheme 11). Compound T-15 was prepared in 52% yield (steps 9, 10), while T-16 was prepared in 68% yield (steps 11, 12). The sulfide contraction method with T-15 and T-16 (step 13) yielded the tetracyclic lactam T-17. Extrusion of cyanide and metalation (step 14) gave T-18, which upon iminoester condensation/cyclization reaction (step 15) afforded the octahydroporphyrin T-19 in 48% overall yield. Demetalation, tert-butyl ether cleavage and retroaldol/oxidation under one arrow (step 16) gave the corresponding bacteriochlorin (tetrahydroporphyrin, T-20) in 42% yield. Finally, manipulation of the C-glycoside group (step 17) and oxidation of the methylene group to create the oxo groups (step 18) afforded the target dioxobacteriochlorin, tolyporphin A O,O-diacetate T-2b (Scheme 11; structures as shown in the original Kishi papers).

The stepwise yields for the synthesis of ring A–D precursors, preparation of AB and CD halves, and coupling of AB and CD halves (step 1–13) are acceptable (47–75%). On the other hand, the yields for the iminoester condensation/cyclization (step 15), conversion from hydroporphyrin to bacteriochlorin (step 16), and oxidation of bacteriochlorin (step 18) proceed in
lower yields (30–48%). On the basis of this reported route, to obtain 1.0 mg of tolyporphin A $O,O$-diacetate (T-2b) would require an estimated 0.62 g of methyl $\alpha$-D-galactopyranoside, 2.63 g of L-(S)-glutamic acid, 0.089 g of $\gamma$-butyrolactone, and 0.11 g of $\alpha$-methyl-$\gamma$-butyrolactone. The cRME for steps 1–18 of the synthesis is $1.2 \times 10^{-4}$; upon inclusion of the preparation of precursors from commercially available starting materials, the cRME is $3.6 \times 10^{-5}$.

Tolyporphin A contains two acetate groups, thus tolyporphin $A\ O,O$-diacetate contains four acetate groups and is a natural product derivative. The revisions required to synthesize the natural product tolyporphin A rather than tolyporphin $A\ O,O$-diacetate may be substantial unless selective cleavage of two of the four acetate groups can be achieved. The installation of the two acetate groups per C-glycoside occurs late in the synthesis (step 17), replacing two $O$-benzyl protecting groups that are carried through three steps leading to pre-T-6a and steps 5–16 thereafter (Schemes 10 and 11). Hence, differential protection of the distinct hydroxy groups – to distinguish the native acetoxy groups versus the free hydroxy groups in tolyporphin A – may need to be introduced at a very early stage and carried through as many as 15 steps. Such differential protection would be essential for syntheses of C-glycosyl-containing tolyporphins B, C, E, F, L and M, whereas tolyporphins D and K exclusively contain free hydroxy groups (lacking any acetoxy groups), but differential protection again would be required for the hydroxy/acetoxy groups attached at the pyrrole ring of tolyporphins E–H (Chart 3).

6 Synthesis heuristics

6.1 Quantitative evaluation – a key metric

The quantitative analyses reported here of chlorophyll $a$, (±)-bonellin dimethyl ester and tolyporphin $A\ O,O$-diacetate should be regarded as a tribute to the masterful if not heroic syntheses in successive eras by the teams led by Woodward, Battersby and Kishi. All three of
the syntheses were successful in accomplishing the objectives of unambiguous structure elucidation and path establishment, despite the more limited capabilities of synthesis science 20–60 years ago. Regardless, none has been used since, let alone serve as a workhorse path for preparation of diverse analogues. The development of a synthetic route connoted by the term “total synthesis” often has included the stitching together of synthetic segments reported in the literature regardless of whether the full path was traversed in a single lab from start to finish. In addition, while relay syntheses were prevalent in the early era of natural products syntheses, many such syntheses have since been replaced with modern (non-relay) routes. The family of (bacterio)chlorophylls and other hydroporphyrins has escaped this attention.

Analysis of the total amount of reactants and reagents (but not solvents, catalysts or purification materials) for the entire synthesis affords a cRME value; the values as reported herein are summarized in Table 2. The cRME’ values, which omit the large excess of reagent in those cases where the reagent also serves as solvent, paint a less severe picture as to the required materials. On the other hand, a true quantitative evaluation would tabulate all ingredients (all solvents and all workup materials), but such data are not available. We recognize that syntheses are judged by multiple metrics – as Nicolau et al. stated,\textsuperscript{103} attractive features include “(i) efficient synthetic reactions; (ii) brevity; (iii) readily available and inexpensive starting materials; (iv) practical and convenient conditions; (v) flexibility of modification in case of pitfalls; (vi) adaptability to the synthesis of other members of the structural family, be they naturally occurring or designed molecules; and (vii) novelty, elegance, and artistry.” We suggest that the cRME provides a valuable and readily accessible \textit{quantitative} metric for gauging the practical utility of a hydroporphyrin synthesis. To prepare 10 mg of a hydroporphyrin with cRME = 10\textsuperscript{-4} would require 100 g of reactants and reagents; a cRME = 10\textsuperscript{-5} would require 1 kg. A practical
synthesis in an academic setting would be possible with cRME = 10⁻⁵ but 10⁻⁴ is certainly preferable.

**Table 2.** Materials required to prepare 1.00 mg of a hydroporphyrin

<table>
<thead>
<tr>
<th>Compound</th>
<th>Key starting compounds</th>
<th>cRME, materialsᵃ</th>
<th>cRME', materialsᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorophyll a</td>
<td>Ethyl acetoacetate</td>
<td>4.3 × 10⁻⁹, 230 kg</td>
<td>1.0 × 10⁻⁹, 100 kg</td>
</tr>
<tr>
<td>(±)-Bonellin dimethyl ester</td>
<td><strong>B-17, B-18, B-19, B-20, B-21</strong></td>
<td>6.4 × 10⁻⁴, 1.56 g</td>
<td>2.2 × 10⁻⁵, 0.45 g</td>
</tr>
<tr>
<td>Tolyporphin A O,O-diacetate</td>
<td>methyl α-D-galactopyranoside, L-(S)-glutamic acid, γ-butyrolactone, α-methyl-γ-butyrolactone</td>
<td>3.6 × 10⁻⁵, 27.8 g</td>
<td>4.1 × 10⁻⁵, 24 g</td>
</tr>
</tbody>
</table>

ᵃ All materials (reactants, reagents) required beginning with the key starting compounds; see text.
ᵇ Any reagents employed as solvents are taken in stoichiometric quantities.

(±)-Bonellin dimethyl ester and tolyporphin A O,O-diacetate have been prepared via total synthesis, whereas the synthesis route to chlorophyll a has not been fully traversed. The syntheses of (±)-bonellin dimethyl ester and tolyporphin A O,O-diacetate were conducted more recently (versus the late 1950s for that of chlorophyll a), hence more extensive starting materials were likely available and known methodologies for small-molecule manipulation were more advanced, which together enabled more concise syntheses. On the other hand, the precipitous decline in yields in the chlorophyll a synthesis campaign generally occurred after macrocycle formation, not in the syntheses of pyrroles or dipyrrromethanes leading to the macrocycle. While acknowledging these distinctions, several insights emerge upon comparison of the syntheses in the context of the cRME assessment.
6.2  Macrocycle formation

The chlorophyll \( a \) synthesis can be divided almost equally into distinct stages: 25 steps for pyrrole and dipyrromethane/dipyrrin syntheses (stages I and II), and 24 steps for macrocycle formation and derivatization (stages III and IV). While chlorophyll \( a \) contains five rings whereas bonellin and tolyporphin A each contain four, the syntheses of (±)-bonellin dimethyl ester and tolyporphin A \( O,O \)-diacetate each employed comparatively few steps on the intact macrocycles. For (±)-bonellin dimethyl ester, 11 steps preceded and 1 step followed macrocycle formation (13 steps in total). For tolyporphin A \( O,O \)-diacetate, 14 steps preceded and 3 steps followed macrocycle formation (18 steps in total). As a general rule, the reactions on the intact macrocycles proceeded in lower yield than those of the smaller precursors. In fact, the steps with lowest yields for each of these three syntheses were all in the macrocycle formation or manipulation stages. This analysis is independent of how the steps are counted (vide infra).

6.3  Precursor reduction level

The (±)-bonellin dimethyl ester and tolyporphin A \( O,O \)-diacetate syntheses employed pre-set gem-dialkyl-substituted pyrrolinic units, in which case reduction would not be required in the final macrocycle. By contrast, the chlorophyll \( a \) synthesis route relied on formation of a porphyrin followed by reduction to the chlorin. The route to tolyporphin A \( O,O \)-diacetate relied on use of lactams or hydropyrrole rings rather than pyrrole units throughout almost the entire route (steps 1–15). Step 17 entailed reaction of the C-glycoside substituents. Only one step was performed on the macrocycle itself (step 18), and this step proceeded in the lowest yield (30%).

6.4  Reactions on macrocycles
A number of ostensibly straightforward reactions on tetrapyrrole macrocycles – on the macrocycle itself or on substituents attached thereto – proved to be problematic in the chlorophyll campaign. The problems could potentially originate from the following:

(i) Low concentrations of tetrapyrrole macrocycles. The concentration of reactions with tetrapyrrole macrocycles is usually more than one or two orders of magnitude lower versus similar reactions with small molecules. Indeed, reactions of tetrapyrroles are typically carried out in the 1–50 mM regime owing to solubility limitations$^{104}$ – for example, the solubility limit in CH$_2$Cl$_2$ at room temperature for meso-tetrakis(R)porphyrin is 0.5–0.7 mM (R = biphenyl)$^{105}$, 25 mM (R = phenyl)$^{106}$, 70–99 mM (R = pentyl)$^{107}$ and 90 mM (R = mesityl)$^{106}$. Such (intermolecular) reactions often result in modest or low efficiency. While specific examples are often hard to identify, it is notable that step 46 (Scheme 6), where nitrile methanolysis of a 1.4 mM solution of chlorin e$_6$ nitrile (45, 9.4 mg in 10 mL of MeOH) proceeded in 36% yield, which is at odds with the typical high yields at molar concentrations.$^{108}$

(ii) Side reactions of tetrapyrrole macrocycles. The macrocycle formation and manipulations consisted of 21 steps (steps 26–46, Schemes 4-6), which included treatment with a strong Brønsted acid (steps 26, 27, 30, 34, 38, 46), strong basic conditions (steps 38, 40, 41) and high temperature (step 37, Scheme 5). These reaction conditions, while quite typical for many aromatic compounds, may give rise to lower yields with (electron-rich) tetrapyrroles due to side reactions (e.g., oxidation, dimerization).

(iii) Isolation of tetrapyrrole macrocycles. In some steps, a high yield was determined for the crude material (via spectroscopy) while a significant loss was observed upon isolation (e.g., steps 39 and 45, Schemes 5 and 6). The presence of tetrapyrrole impurities with structures closely related to that of the desired reaction product can lead to recalcitrant separations, the
protracted nature of which gives rise to inevitable losses. Decomposition during isolation (often chromatography or recrystallization) also can occur due to photochemical oxidation.

It warrants pointing out that with no intellectual advance in synthesis methods, mere use of modern isolation techniques (e.g., preparative HPLC) may provide a much better scenario for the stereoisomer resolution. If so, improving the resolution (step 42, 4%, Scheme 5) to the maximum yield (50%) and thereby likely also omitting step 41 (60%) would then require 706 g (instead of 14.7 kg) of ethyl acetoacetate to achieve 1 mg of chlorophyll \(a\). Beyond technological improvements, the chlorophyll synthesis program was carried out prior to the advent of the field of stereoselective synthesis; judicious use of stereoselective steps may provide further improvements.

### 6.5 Number of steps

The comparison of synthetic routes on the basis of the number of steps can be quite misleading, given that several reaction steps can be written over a given arrow thereby affording the appearance of a shorter route versus one where each individual step bears a corresponding arrow. For example, the portrayal of the chlorophyll \(a\) synthesis largely described a single molecular transformation per reaction arrow whereas the tolyporphin A \(O,O\)-diacetate synthesis often displayed multiple transformations per arrow, and in some cases performed workup procedures between transformations all of which appear with a given arrow. Hence the actual length of the tolyporphin A \(O,O\)-diacetate synthesis is substantially greater than indicated by the count of 18 steps. Regardless of display, the cRME value is essentially unchanged. The relative “length” of the two syntheses is a reflection of this representation and implementation, but the distinction in cRME values is independent thereof.
7  **Outlook**

In summary, the synthetic chemistry of (bacterio)chlorophylls is embryonic, as no fully traversed synthesis is known. Routes to (±)-bonellin dimethyl ester and tolyporphin A $O,O$-diacetate have been established, but access to the native macrocycles bonellin and tolyporphin A remains to be developed. Doing so likely will require substantial revisions to the aforementioned synthetic routes, requiring an enantioselective route to bonellin and provisions for incorporating the two $O$-acetate groups and two hydroxy groups in tolyporphin A. The synthesis of the growing family of tolyporphins (B–M) remains unexplored; indeed, even many stereochemical features have not been established for the natural products. The design of a practical total synthesis of such hydroporphyrins likely should create the macrocycle as late as possible in the overall synthetic plan. Such an approach requires reliance on precursors at the same reduction level as in the target macrocycle and the pre-installation of peripheral substituents prior to macrocycle formation to the extent possible.

An alternative approach for preparation of natural chlorins relies on semisynthesis from protoporphyrin IX (the free base ligand of heme) – readily available from an abattoir or via a robust scalable synthesis$^{109}$ – a notable target prepared in this manner is the chlorin heme $d$. $^{110}$

Many of the objectives outlined in the Introduction that motivate the synthesis of natural hydroporphyrins and analogues would require full traversal of the synthesis (small commercially available compounds $\rightarrow$ protoporphyrin IX $\rightarrow$ natural hydroporphyrin) rather than the academic stitching together of two distinct reported syntheses. While the robustness of protoporphyrin IX would appear to make such a total synthesis possible, an approach to implement a total synthesis beginning with small commercially available compounds might not proceed via the protoporphyrin IX waystation. Regardless, for implementation in laboratories in academia or research institutes, a $cRME > 10^{-5}$ (preferably $10^{-4}$) would appear to be essential. The
availability of such enabling total syntheses would have a profound impact in a broad range of scientific areas beyond that of synthesis itself, making diverse (bacterio)chlorophylls, other hydroporphyrins and analogues readily available for the wide range of studies typically engendered by synthetic natural products chemistry. In this regard, the natural hydroporphyrins would no longer be an abandoned or bypassed partner in the mutually enriching dance with synthetic chemistry.

8 Conflicts of interest

The authors declare no conflicts of interest.

9 Acknowledgements

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10 References


**Supporting Information:** An example scaling calculation of the cRME.
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Yizhou Liu (b. 1990) grew up in Mianyang, China and obtained his Bachelor’s degree in Chemistry from Peking University in 2012. In 2018, he received his PhD degree in organic chemistry from North Carolina State University with Professor Jonathan Lindsey. His research interests range from metal-mediated coupling reactions to tetrapyrrole synthesis. In addition to chemistry, Yizhou is an active software developer and studies data science.
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Jonathan S. Lindsey (b. 1956) grew up in Rockport, Indiana and did his undergraduate studies at Indiana University in Bloomington (1974–1978) where he worked with Profs. Frank R. N. Gurd and Lawrence K. Montgomery. His graduate and postdoctoral studies (1978–1984) were at The Rockefeller University with Prof. David C. Mauzerall in the Laboratory of Photobiology. He was on the faculty at Carnegie Mellon University for 12 years before joining North Carolina State University in 1996. His interests include the science of tetrapyrroles and their roles in photosynthesis; the origins and scope of molecular biodiversity; and biomedical science.