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Synthesis of tailored hydrodipyrrins and their examination in directed routes to bacteriochlorins and tetradehydrocorrins†

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The chemistry of reduced tetrapyrroles is less developed than that of the fully unsaturated (porphyrin) analogues, yet is of comparable importance given the natural roles of hydroporphyrins (*e.g.*, chlorophylls, bacteriochlorophylls) and contracted hydroporphyrins (cobalamin). The self-condensation of a 1-(dimethoxymethyl)-2,3-dihydro-3,3-dimethyldipyrrin (termed a dihydrodipyrrin-acetal) affords the corresponding bacteriochlorin or tetradehydrocorrin with the outcome potentially controllable by choice of the catalysis conditions. The ability to install distinct patterns of substituents about the perimeter of the synthetic macrocycles is essential for biomimetic studies. Here, 18 new target (and 9 intermediate) hydrodipyrrins encompassing a range of dipyrrin saturation levels (dihydro, tetrahydro, hexahydro) and equipped with diverse α-pyrrole (-H, -SMe, -SPh, -Br, -Me, -CO_2R, dioxaborolanyl) and α-pyrroline (methyl, formyl, dimethoxymethyl, oxo, methoxy, methylthio, iminomethyl, ethoxycarbonylvinyl, dicyanovinyl) substituents have been prepared and examined in the directed synthesis of bacteriochlorins. The routes – inspired by a directed route to chlorins – rely on condensation of two hydrodipyrrins to produce a hydrobilin followed by ring closure to form the macrocycle. Four new unsymmetrically substituted bacteriochlorins were obtained in very low yields; as an offshoot, efficient routes to three new tetradehydrocorrins (nickel chelates) were discovered, including two *B,D*-tetradehydrocorrins (pyrroline–pyrrole A–D ring junction) and one *B,C*-tetradehydrocorrin (pyrroline–pyrroline A–D ring junction). Taken together, this study deepens our understanding of the chemistry of hydrodipyrrins and hydrobilins as precursors to hydroporphyrins.

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Introduction

Hydroporphyrins play central roles in biological energy transduction and in catalysis yet have been far less examined than porphyrins from the standpoint of synthesis and model systems chemistry. The comparative deficiency stems from the relative ease of the synthesis of the respective macrocycles. The hydroporphyrins of interest include chlorins and bacteriochlorins, which absorb in the red and near-infrared spectral regions, and are dihydroporphyrins and tetrahydroporphyrins, respectively.[1,2] A more expansive, yet less explored, set of hydroporphyrins entails the ring-contracted macrocycles ranging from octadehydrocorrins to corrins. Of particular interest here are bacteriochlorins, which constitute the fundamental macrocycle of bacteriochlorophylls, and their counterpart in the ring contracted series, tetradehydrocorrins (Scheme 1). The latter stand halfway between the fully unsaturated macrocycle, an octadehydrocorrin[3–5] and the $8e^-$, $8H^+$ reduced macrocycle, a corrin. An octadehydrocorrin is a formal tautomer of the well-known corrole. While corroles[6,7] and corrins[8–11] have been extensively studied, the reduced analogues intermediate between corroles and corrins have received less attention owing to synthetic challenges given the complexity of the macrocycles.[12]

Early syntheses of bacteriochlorins have relied on hydrogenation of (or addition to) synthetic porphyrins and chlorins.[13–15] The first *de novo* synthesis of bacteriochlorins targeted an analogue of the naturally occurring (but likely non-photosynthetic) bacteriochlorin tolyporphin A (Scheme 2A).[16,17] While an elegant solution for the architecturally complex macrocycle, the length of the synthesis has stymied applications to a broader set of bacteriochlorins. The *de novo* synthesis (Scheme 2B, top) of non-natural bacteriochlorins relies on the self-condensation of a dihydrodipyrrin-acetal[18,19] or dihydrodipyrrin-carboxaldehyde,[20] and is compatible with diverse substituents at the β-pyrrolic positions.

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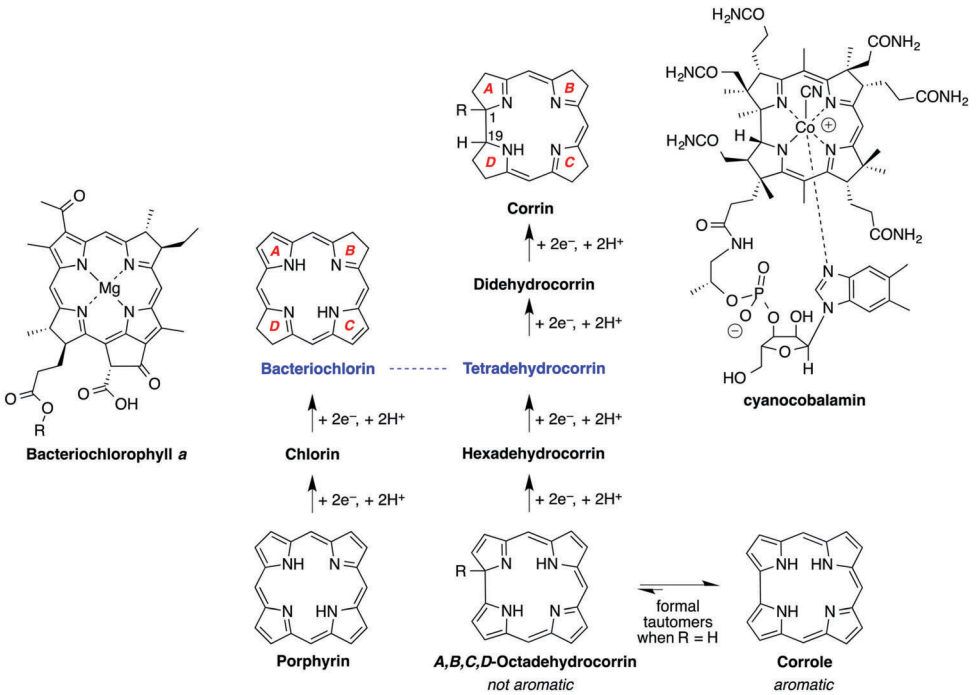
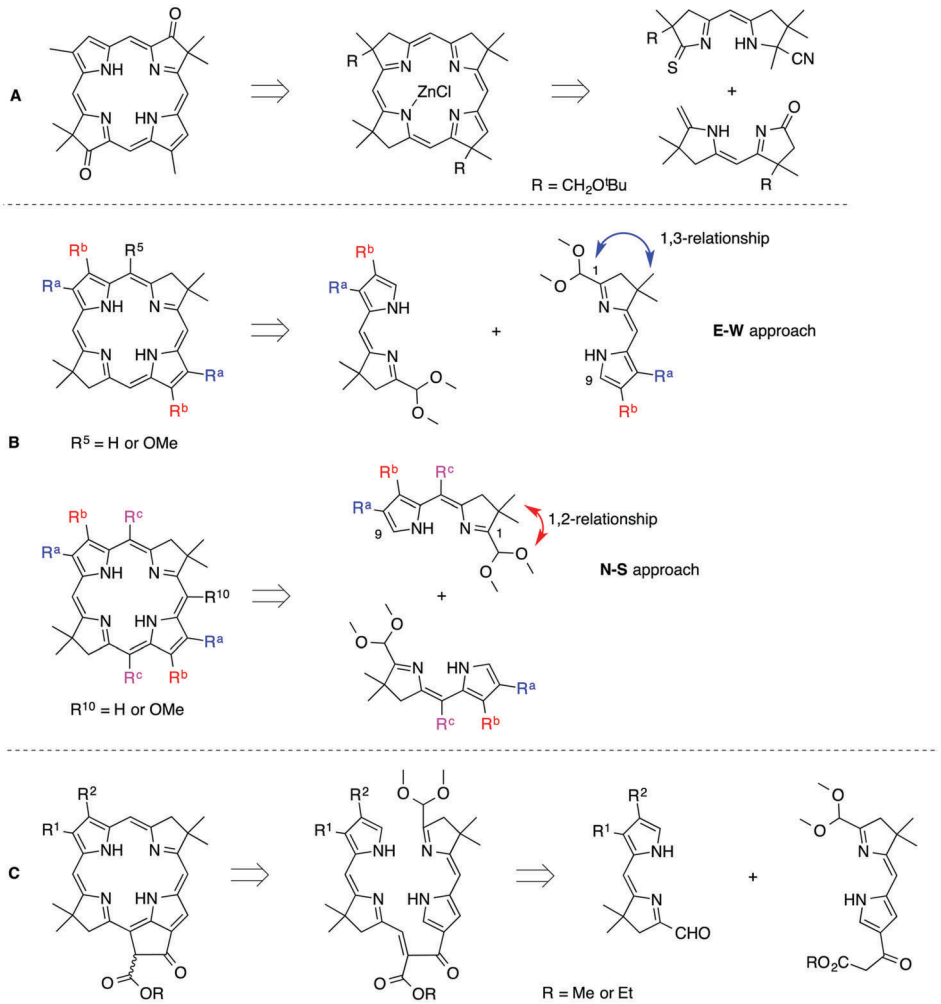


Scheme 1 Natural hydroporphyrins (bacteriochlorophyll *a*, cobalamin), and equivalence of bacteriochlorin and tetradehydrocorrin saturation levels.

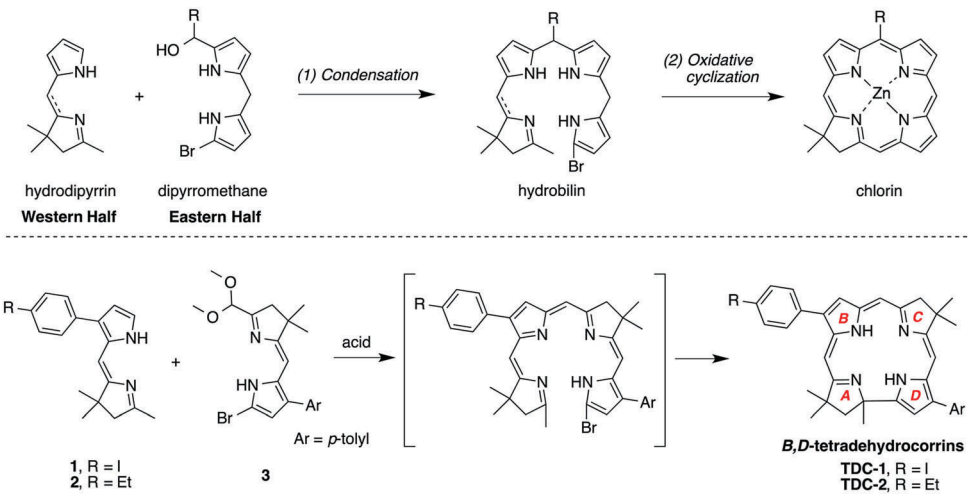
A complementary route (Scheme 2B, bottom) employs a Northern–Southern (N–S) self-condensation of a dihydrodipyrrin-acetal, which affords the same bacteriochlorins as the Eastern–Western (E–W) route but the structure and method for construction of the dihydrodipyrrin-acetals more readily enable incorporation of *meso*-substituents,[21] although *meso*-phenyl groups have recently been incorporated *via* the E–W route.[22] The key structural difference between the dihydrodipyrrins for the E–W and N–S route is the location of the gem-dimethyl group at the 3- or 2-position relative to the 1-(dimethoxy)methyl unit. A recent *de novo* route constructs the bacteriochlorin macrocycle as well as the isocyclic ring in a one-flask reaction from a linear tetrapyrrole, which includes Nazarov cyclization and electrophilic aromatic substitution (Scheme 2C). The linear tetrapyrrole in turn is prepared by Knoevenagel condensation starting from two dihydrodipyrrins.[23] Each bacteriochlorin shown in Scheme 2 contains a gem-dialkyl group in each pyrroline ring; the gem-dialkyl group blocks adventitious dehydrogenation.[24] Inspection of all of the routes in Scheme 2 shows the critical importance of access to hydrodipyrrins bearing a gem-dialkyl group in the pyrroline ring and distinct substituents at the respective α-positions of the pyrrole and pyrroline units.[25]

An unmet challenge in bacteriochlorin synthesis concerns access to unsymmetrically substituted macrocycles with diverse groups on the respective pyrrole and pyrroline rings. In the synthesis of chlorins, which contain only one pyrroline ring, the use of a hydrodipyrrin Western half and a dipyrromethane Eastern half naturally affords a directed synthesis (Scheme 3, top).[24] Accordingly, unsymmetrically substituted chlorins are readily available by virtue of the substitution of the respective distinct halves. We attempted to extend the features of the chlorin synthesis through an analogous directed synthesis of bacteriochlorins, where both reacting halves were necessarily dihydrodipyrrins. The terminal substituents of the two hydrodipyrrins for the Western half (**1** or **2**) and Eastern half (**3**) were chosen – by analogy with the chlorin synthesis – such that neither could undergo self-condensation (Scheme 3, bottom).[26] Yet, treatment with a Lewis acid did not give the desired linear tetrapyrrole (a hydrobilin), but rather a green product that was found to be a *B*,*D*-tetradehydrocorrin (**TDC-1**, **TDC-2**) bearing a methyl group at the A–D ring junction. The *B*,*D*-tetradehydrocorrins contain a linear polyene chromophore (coincidentally embedded in a macrocycle) and as such lack the intense absorption characteristics of bacteriochlorins.[18] The *B*,*D*-tetradehydrocorrin macrocycle is known as a competing byproduct with bacteriochlorins upon E–W dihydrodipyrrin-acetal self-condensation under certain acid-catalysis conditions,[27] yet in the directed reaction attempted here the *B*,*D*-tetradehydrocorrin was the sole macrocycle obtained. Tetradehydrocorrins are potentially valuable ligands for studies in catalysis, given the rich chemistry of the natural corrins,[8,9,11] although the cobalt complex of **TDC-2** proved to be unstable toward electrochemical cycling.[26]

The aforementioned precedents suggested that investigation of a set of hydrodipyrrins bearing a broader selection of terminal (1,9-, or α-) substituents might lead to unsymmetrically substituted bacteriochlorins rather than tetradehydrocorrins, and also that more stable tetradehydrocorrins would likely require an A–D ring junction between two pyrrolines rather than one pyrroline and one pyrrole. The exploration of routes to such architectures requires access to new hydrodipyrrins. In this paper, we describe the synthesis of hydrodipyrrins bearing a variety of terminal substituents, and exploratory studies of directed syntheses of



Scheme 2 Building bacteriochlorin macrocycles: (A) Kishi's route to tolyporphin A analogues,[16,17] (B) the Eastern–Western strategy (top)[18–20] and Northern–Southern strategy (bottom),[21] and (C) the Knoevenagel–Nazarov strategy.[23]



Scheme 3 Directed route to chlorins (top) and attempted analogous route for bacteriochlorins that instead afforded *B,D*-tetradehydrocorrins (bottom).

bacteriochlorins. The paper is divided into three parts. In part I, we describe the preparation of 10 target hydrodipyrrin building blocks, which bear distinct groups at the α-pyrrole or α-pyrroline position; the synthesis[28–32] and examination of 8 other target

hydrodipyrrin building blocks is described in the ESI.† Altogether 27 hydrodipyrrins have been prepared (including 9 intermediates), which extends a collection of 33 hydrodipyrrins prepared previously.[25] Part II describes the use of the 10 hydrodipyrrin building blocks in approaches to bacteriochlorins as well as ring-contracted analogues, namely tetradehydrocorrins. The synthetic route to bacteriochlorins remains based on the *de novo* route to chlorins. Part III describes the chemical characterization of the resulting new bacteriochlorins and tetradehydrocorrins.

Results and discussion

Reconnaissance

The directed joining of two dipyrrolic species in the synthesis of chlorins begins by condensation at the α-pyrrole position of the dipyrromethane and the α-substituent (carboxaldehyde or carbinol) of the hydrodipyrrin to form a linear tetrapyrrole (a hydrobilin[33,34]); subsequent metal-mediated oxidative cyclization gives the chlorin. While very little is known about the exact sequence of steps and the reactivity of specific intermediates in the oxidative cyclization,[35] the process is reliable with good overall efficiency.

In the chlorin synthesis, four distinct terminal substituents (pyrrole-H, pyrroline-CH_3/enamine, pyrrole-CHR(OH), pyrrole-Br) are present, two of which carry a substituted methyl group destined to become a *meso* carbon (Scheme 3, top). In the undirected E–W and N–S routes to bacteriochlorins, one dihydrodipyrrin undergoes self-condensation, wherein only two distinct terminal substituents are present (pyrrole-H, pyrroline-$CH(OMe)_2$), one of which is the latent *meso* carbon (Scheme 2B). A directed synthesis of bacteriochlorins requires two hydrodipyrrins with four distinct terminal substituents. Many combinations are possible of terminal substituents (W, X, Y, Z), and the saturation level can be di-, tetra-, or hexa-hydrodipyrrin (Scheme 4), yet the *sine qua non* is that (1) a pair of substituents on a given hydrodipyrrin (W,X; Y,Z) must be incompatible with self-condensation, (2) one of W,X and one of Y,Z (or both of one pair and neither of the other pair) must convey a *meso* carbon to complete the macrocycle, and (3) W must react with/at Y not Z, and X must react with/at Z not Y.

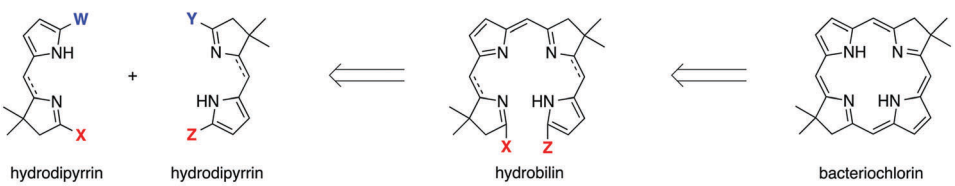
To explore various directed routes, 18 target hydrodipyrrins have been prepared as well as nine intermediates or byproducts (27 hydrodipyrrins altogether). Chart 1 shows ten target hydrodipyrrins (**4a–c**, **4c-Im**, **5a**, **5b**, **6–9**) that led to a successful reaction, eight hydrodipyrrins (**S1–S8**) that did not prove fruitful in macrocyclization, and three hydrodipyrrin targets (**T1–T3**) that were sought but to date have not been prepared. The syntheses of **S1–S8**, exploratory routes to **T1–T3**, and exploratory routes to bacteriochlorins using **S1–S8** are described in the ESI.† Among the eighteen new hydrodipyrrins, the dihydrodipyrrins wherein the pyrroline "X,Y" substituent contains an electrophilic single carbon include OHC– (**4a-c**, **7**), $(MeO)_2CH$– (**5a**, **5b**, **6**, **S4**, **S5**), and *tert*-butyliminomethyl (**4c-Im**); those that contain an electrophilic pyrroline position (no carbon substituent) include **S6–S8**; and those that contain an electrophilic alkenyl moiety include **8**, **S2** and **S3**. Compound **S1** is a tetrahydrodipyrrin that bears a $(MeO)_2CH$– substituent at the pyrroline position, whereas **9** is a tetrahydrodipyrrin that bears a methyl substituent at the pyrroline 1-position. The pyrrole "W,Z" substituents include ethoxycarbonyl (**4a**, **5a**), methyl (**4b**, **5b**), H– (**4c**, **4c-Im**, **8**, **9**, **S1**, **S2**, **S6–S8**), *tert*-butoxycarbonyl (**S3**), methylthio (**6**), phenylthio (**S4**), bromo (**7**), and borolanyl (**S5**). Other pyrrole substituents were incorporated to explore reactivity features, to facilitate synthesis, or based on the availability of reactants. Some of the hydrodipyrrins resemble traditional Eastern or Western halves in chlorin chemistry whereas others do not; in general, such distinction is less meaningful here given that the bacteriochlorin (or tetradehydrocorrin) contains two pyrroline and two pyrrole units, and each hydrodipyrrin contains one pyrroline and one pyrrole unit.

The nomenclature of hydrodipyrrins is displayed at the bottom of Chart 1. In addition to the change in saturation level indicated by di-, tetra-, and hexa-hydro prefixes, a further distinction concerns the location of the gem-dimethyl group on the pyrroline ring. Two routes have been employed for construction of the hydrodipyrrins,[24] which stem from the pioneering work of teams led by Battersby and by Jacobi. The Battersby route[36] affords the 3,3-dimethyl substituent pattern whereas that of Jacobi[28] affords the 2,2-dimethyl pattern.

Synthesis of hydrodipyrrins

The synthesis of tetrahydrodipyrrins bearing 1-methyl groups is well established.[37] Here, reductive cyclization of nitrohexanone **10**[20] in the presence of zinc dust and ammonium acetate in THF gave tetrahydrodipyrrin **9** in 63% yield (Scheme 5, lower right).

Several new dihydrodipyrrins were prepared that contain blocking units (to prevent self-condensation) at the α-pyrrole position; such groups were introduced at the beginning of the route (Scheme 5, left). Pyrrole–carboxaldehydes **11a**,[38] **11b**,[39] and **11c**[19] are known; **11a** and **11b** were prepared in a two-step procedure starting from a Paal–Knorr synthesis, whereas **11c**



Scheme 4 Hydrodipyrrin terminal substituents W, X, Y, and Z in a directed synthesis of bacteriochlorins.

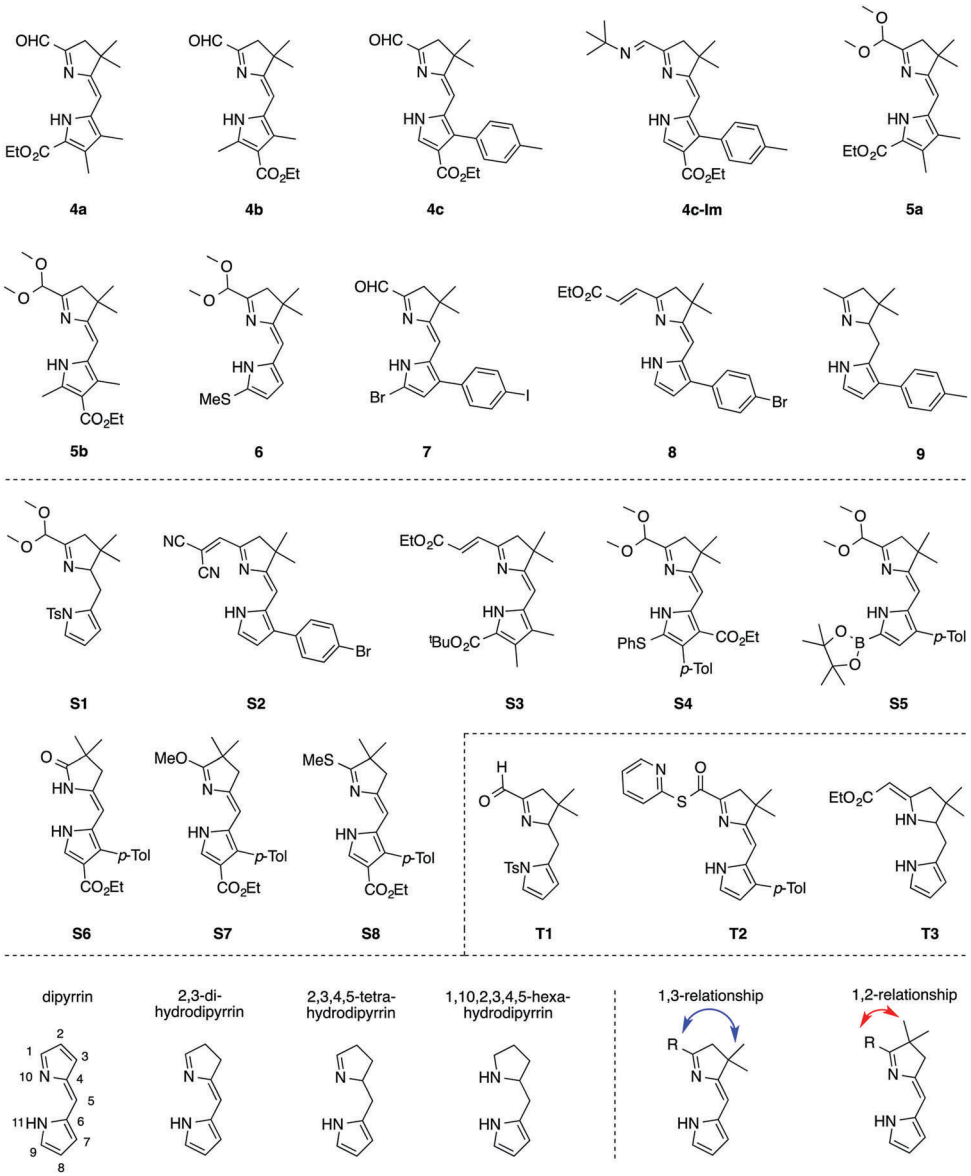
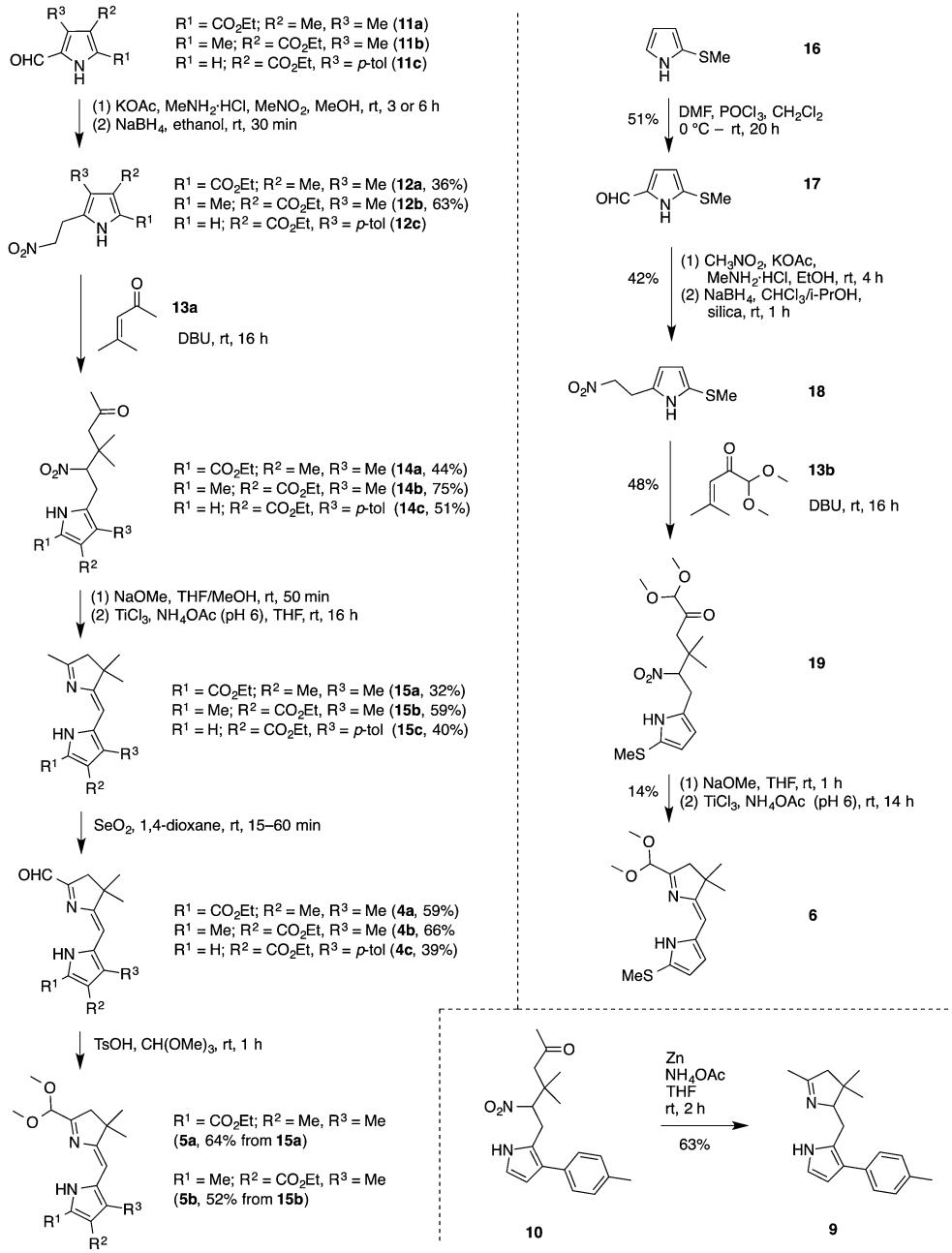


Chart 1 Eighteen hydrodipyrrins prepared for studies of macrocycle formation (**4a–8**, **S1–S8**; top and middle). Three desired target hydrodipyrrins (**T1–T3**, middle right). Dipyrrin and hydrodipyrrin nomenclature (bottom).

was prepared in a two-step procedure starting from a van Leusen synthesis. The electron-withdrawing ethoxycarbonyl group stabilizes the pyrrole ring during subsequent transformations. Pyrrole–carboxaldehydes **11a–c** were converted[19] to nitroethylpyrroles **12a–c** *via* a Henry reaction and reduction with $NaBH_4$. Treatment of **12a–c** with α,β-unsaturated ketone mesityl oxide (**13a**) in the presence of DBU at room temperature afforded the corresponding nitrohexanones **14a–c**. Subsequent $TiCl_3$-mediated reductive cyclization afforded dihydrodipyrrins **15a–c**, which upon oxidation with SeO_2 gave dihydrodipyrrin-carboxaldehydes **4a–c**.[20] Aldehydes **4a,b** were converted to the corresponding dihydrodipyrrin-acetals **5a,b** by exposure to trimethyl orthoformate in the presence of *p*-toluenesulfonic acid (TsOH).[21] Dihydrodipyrrin-acetal **5c** (the dimethyl acetal of **4c**) was prepared previously by Michael addition of the required 2-(2-nitroethyl)pyrrole with the α,α-dimethoxy derivative of mesityl oxide (**13b**).[19]

Dihydrodipyrrin-acetal **6** bears a methylthio group as the pyrrole blocking unit (Scheme 5, right). Thus, 2-methylthiopyrrole **16**[40] underwent formylation selectively at the 5-position to give **17**, which upon Henry reaction and reduction gave the corresponding (2-nitroethyl)pyrrole **18**. Then, **18** was reacted with 1,1-dimethoxy-4-methyl-3-penten-2-one (**13b**),[41] giving nitrohexanone **19** in 48% yield. $TiCl_3$-Mediated reductive cyclization gave dihydrodipyrrin-acetal **6**. The methylthio group has been used as a protecting group for the pyrrole α-position in porphyrin chemistry.[40,42]

The bromination of known hydrodipyrrin-carboxaldehyde **20**[20] was achieved most effectively by using 1 molar equivalent of NBS in THF at −78 °C, affording **7** in 45% yield (Scheme 6).



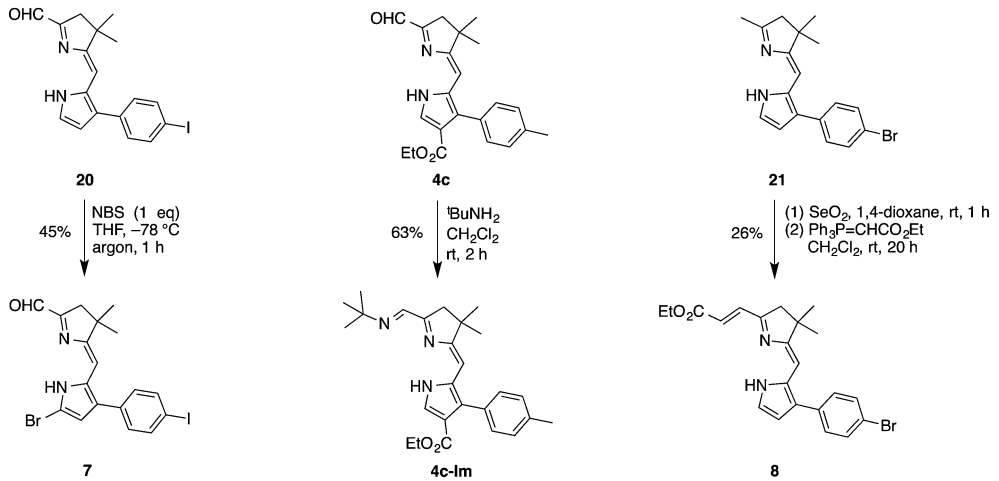
Scheme 5 Synthesis of hydrodipyrrins.

The successful reaction required the use of quite dilute conditions (~10 mM). Compound 7 was prone to decomposition upon dissolution in chlorinated solvents and during chromatography on silica, and slowly decomposed in the solid state at room temperature. On the other hand, 7 was stable for weeks in the solid state at −20 °C, and could be weighed out at room temperature without special precautions. Treatment of the dihydrodipyrrin-carboxaldehyde **4c** with *t*-BuNH$_2$ in dichloromethane at room temperature for 2 h gave the corresponding dihydrodipyrrin-imine **4c-Im** in 63% yield. The imine (a yellow solid) was quite stable compared to the precursor carboxaldehyde (a yellow oil).

The ability to oxidize the 1-methyl group of a dihydrodipyrrin[20] opened the opportunity to elaborate the resulting 1-carboxaldehyde. Thus, the reaction of **21**[23] with SeO_2 followed by methenylation with $Ph_3P{=}CHCO_2Et$ afforded the corresponding dihydrodipyrrin (**8**) bearing an ethyl acrylate moiety at the 1-position (Scheme 6).

Exploration of hydrodipyrrin macrocyclizations leading chiefly to bacteriochlorins

Ten new hydrodipyrrins (Chart 1) were employed here along with four prior hydrodipyrrins (**3**,[26] **5c**,[19] **21**,[23] **22**[20]) in studies of bacteriochlorin and tetradehydrocorrin formation. We first present reactions that mainly afforded bacteriochlorins.



Scheme 6 Manipulation of dihydrodipyrrin-carboxaldehydes (left and center), and extension at the 1-methyl site of a dihydrodipyrrin (right).

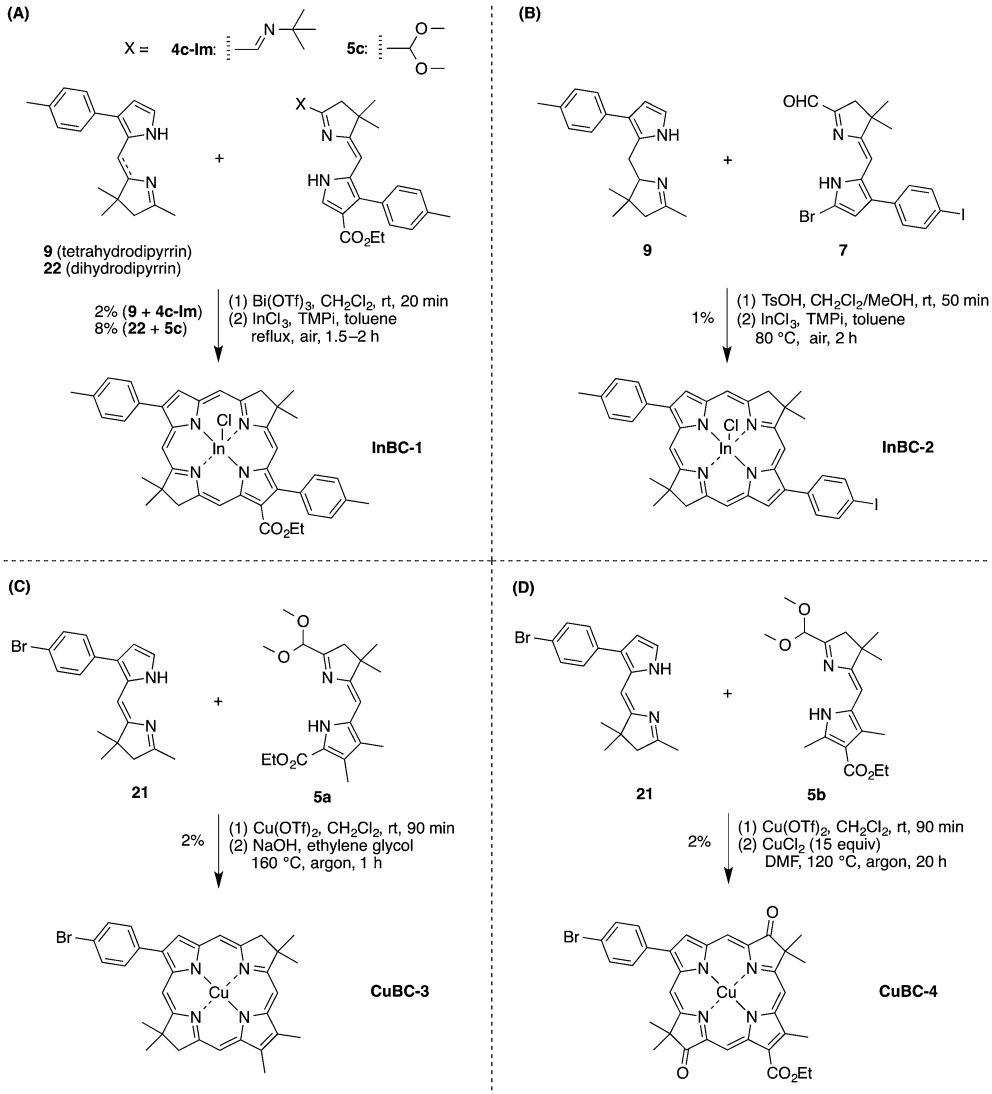
Dihydrodipyrrins without a pyrrole blocking unit. The condensation of **22** (a dihydrodipyrrin) and **5c** was carried out with the expectation that the electron-withdrawing group (–CO_2Et) at the β-pyrrole position in dihydrodipyrrin **5c** would decrease the reactivity of the pyrrole ring and perhaps thereby suppress the self-condensation of **5c**. The reaction was carried out in a two-step process of acid-catalyzed condensation followed by metal-templated oxidative cyclization (Scheme 7A). The reaction mixture was examined by absorption spectroscopy and laser-desorption mass spectrometry (LD-MS). The best result was achieved with condensation at room temperature in CH_2Cl_2 containing $Bi(OTf)_3$ followed by treatment with 10 molar equiv. of $InCl_3$ and 10 molar equiv. of 2,2,6,6-tetramethylpiperidine (TMPi) in CH_3CN or toluene under reflux exposed to air (see the ESI† for survey conditions). The resulting unsymmetrically substituted bacteriochlorin **InBC-1** was obtained in 8% yield (estimated spectroscopically[43]). Some amount of tetradehydrocorrin and a trace amount of a free base bacteriochlorin (obtained from the self-condensation of **5c**) were also observed.

The dihydrodipyrrin-imine **4c-Im** was examined in condensation with tetrahydrodipyrrin **9** in the presence of $Bi(OTf)_3$, followed by cyclization using $InCl_3$/TMPi in refluxing toluene, whereupon **InBC-1** was obtained in 2% yield (Scheme 7A). The tetrahydrodipyrrin **9** is ostensibly more nucleophilic than the analogous dihydrodipyrrin **22**, and the imine **4c-Im** is potentially more directly reactive than the acetal **5c**. Screening of several factors (*e.g.*, concentration of reactants, equivalents of metal triflates), however, did not lead to improved yields.

Hydrodipyrrins with various blocking units. The reaction of a dihydrodipyrrin-acetal with a 1-methyldihydrodipyrrin afforded a tetradehydrocorrin (Scheme 3).[26] Here, 1-methyltetrahydrodipyrrin **9** was examined instead of a 1-methyldihydrodipyrrin (Scheme 7B). The reaction of **9** with dihydrodipyrrin-carboxaldehyde **7** was examined under various conditions, which entailed TsOH·H_2O (5 equiv.) in CH_2Cl_2/methanol at room temperature for the condensation (akin to that in the *de novo* synthesis of chlorins[44]), and thermal cyclization under the above conditions ($InCl_3$/TMPi in toluene at 80 °C). The best conditions afforded **InBC-2** in only 1% yield (estimated spectroscopically[43]).

Montforts and Kutzki reported a synthetic route to chlorins from a linear tetrapyrrole–metal complex, wherein an ester group served as a blocking unit and then was cleaved in refluxing 1,2,4-trichlorobenzene (214 °C).[45] Treatment of dihydrodipyrrin **21** and dihydrodipyrrin-acetal **5a** in dichloromethane with $Cu(OTf)_2$ gave a copper(II) complex as a red-purple gel (Scheme 7C). The copper(II) complex is paramagnetic and so a meaningful ^{1}H NMR spectrum could not be obtained, but it was characterized by mass spectrometry (LD-MS and ESI-MS). The absorption spectrum of this complex in dichloromethane displayed a weak broad band in the 450–600 nm region (ESI†). The complex was robust, as treatment with TFA/H_2SO_4 containing a few drops of 1,3-propanedithiol, conditions known to demetalate copper chlorins,[46,47] did not cause demetalation. Treatment of the copper-complex with sodium hydroxide at high temperature gave the corresponding copper(II)bacteriochlorin **CuBC-3**. Several reaction variables, including temperature, solvents or inert environment, were examined. The highest yield (2%, estimated spectroscopically[48]) was obtained in degassed ethylene glycol at 160 °C under argon. The major by-products detected (by absorption spectroscopy and LD-MS) appeared to be oxobacteriochlorins and tetradehydrocorrins. Attempted demetalation of **CuBC-3** by using TFA/concentrated H_2SO_4/1,3-propanedithiol caused decomposition of the bacteriochlorin.

The cyclization of a 1,8-dimethyl-*a*,*c*-biladiene in refluxing DMF containing a copper(II) reagent is an established approach to the corresponding copper(II)porphyrin.[49] An analogous ring-closure strategy for forming a bacteriochlorin was examined here. First, condensation of **21** and **5b** in the presence of $Cu(OTf)_2$ in CH_2Cl_2 for 2 h gave a copper(II)-complex as a red-purple gel, which was characterized by mass spectrometry and absorption spectroscopy. Subsequent heating in DMF containing $CuCl_2$ (15 equiv.) gave the corresponding dioxobacteriochlorin **CuBC-4** (Scheme 7D) in 2% overall yield (estimated spectroscopically[48]). Battersby *et al.* reported a similar observation in studies of the conversion of tetrahydrobiladienes to the corresponding chlorin, wherein a copper(II)oxochlorin was obtained.[47] In short, each of the routes shown in Scheme 7



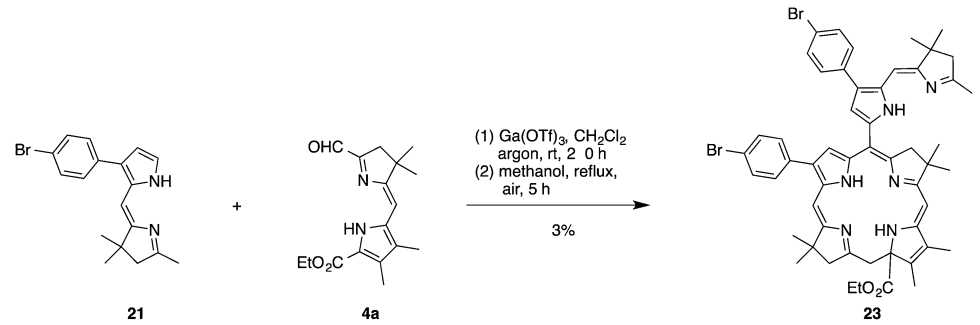
Scheme 7 Routes to metallobacteriochlorins.

affords a bacteriochlorin (or dioxobacteriochlorin) albeit in minuscule yield.

We next explored a synthetic route to bacteriochlorins using **4a** and **21**. The acids that were examined for the condensation included $BF_3{\cdot}OEt_2$, $Sc(OTf)_3$, $Bi(OTf)_3$, $Ga(OTf)_3$, $InCl_3$, $Yb(OTf)_3$, TMSOTf/2,6-di-*tert*-butylpyridine (DTBP) and TFA. Reactions were conducted with 10 mM dihydrodipyrrin (**21** and **4a**, 0.010 mmol scale) and 20 mM acid in CH_2Cl_2 (except for $BF_3{\cdot}OEt_2$ in CH_3CN) with monitoring by LD-MS and absorption spectroscopy. The targeted hydrobilin was not detected under these conditions; a trace amount of the major component was isolated and characterized by LD-MS (found m/z = 966) and absorption spectroscopy. To verify this observation, a condensation was carried out of two molar equiv. of **21** and one molar equiv. of **4a** catalyzed by $Ga(OTf)_3$, followed by aeration in refluxing methanol (Scheme 8). Chromatography afforded (3% yield) a blue-green compound, which was characterized by ^{1}H NMR spectroscopy (methine and pyrrolic protons at δ 4.88, 5.71, 5.90, 6.34, and 6.87 ppm) and ESI-MS. The absorption spectrum in dichloromethane showed an intense band around 333 nm and a broad intense band ranging from 500–700 nm. The sum of all the spectroscopic evidence led to the unusual 1,20-dihydrobacteriochlorin **23**.

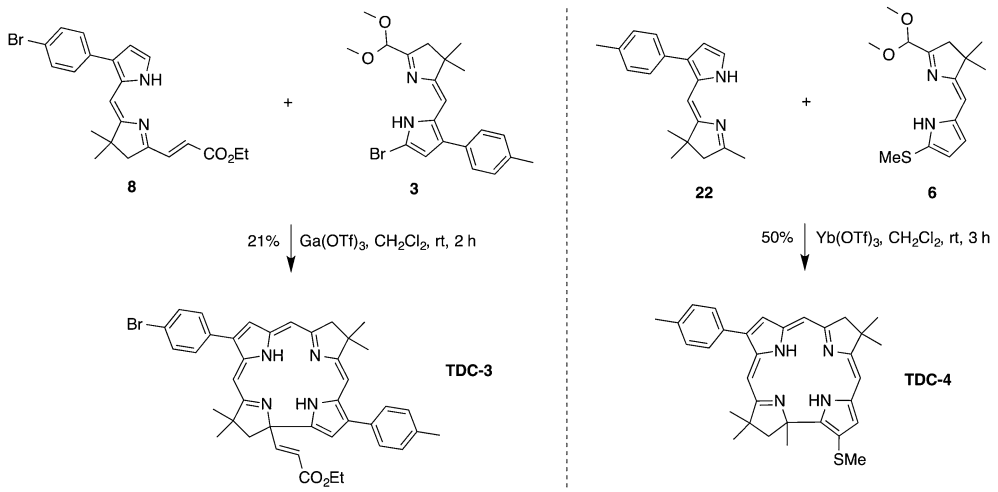
Exploration of hydrodipyrrin macrocyclizations leading chiefly to *B*,*D*-tetradehydrocorrins

Hydrodipyrrin with 1-acrylate for directed reaction. The reaction leading to tetradehydrocorrins entails attack of the pyrrole of one hydrodipyrrin on the imine carbon of a second hydrodipyrrin (Scheme 3). To direct reaction at the 1-carbon substituent (destined to become the *meso*-carbon) and thereby construct the bacteriochlorin macrocycle, a dihydrodipyrrin (**8**) was employed wherein a Michael-like acceptor is located at the 1-position (Scheme 9, left). The Michael acceptor is ethyl acrylate, in which case nucleophilic attack is expected at the β-position of the α,β-unsaturated ester *versus* the pyrroline imine carbon. The reaction of **8** with 9-bromodihydrodipyrrin-1-acetal **3** parallels that leading to **TDC-1** or **TDC-2** but was expected to afford the corresponding bacteriochlorin bearing a $-CH_2CO_2Et$



21 4a 23

Scheme 8 Frustrated route to bacteriochlorins.



8 3 22 6

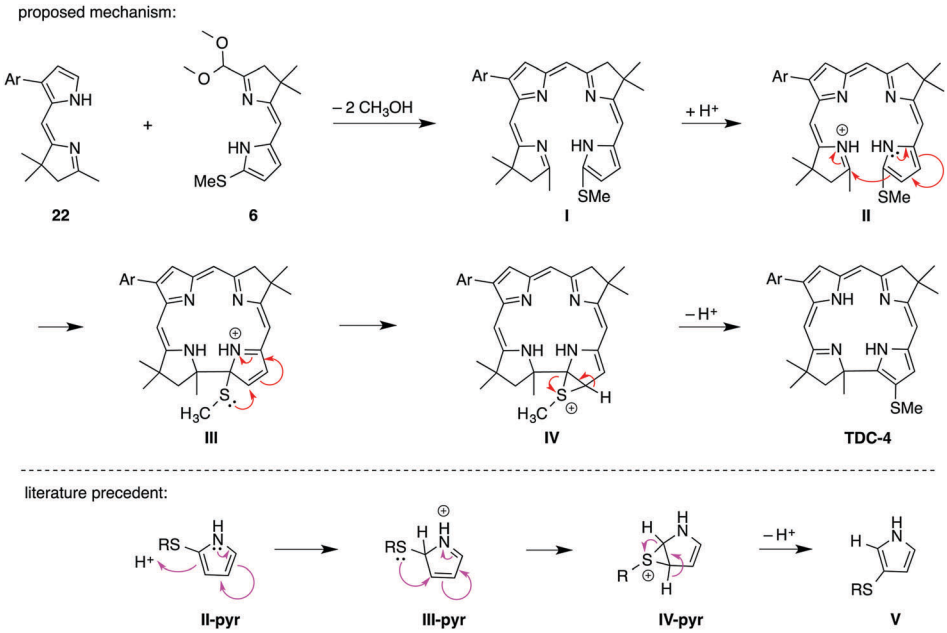
Scheme 9 Formation of new *B*,*D*-tetradehydrocorrins.

substituent at the 15-position. The reaction catalyzed by $Ga(OTf)_3$ afforded the *B*,*D*-tetradehydrocorrin **TDC-3** rather than the desired bacteriochlorin. Attempted rearrangement (under diverse acids[27]) of the tetradehydrocorrin to the corresponding bacteriochlorin failed. Such rearrangement has been demonstrated previously for tetradehydrocorrins that bear a dimethoxymethyl unit at the 19-position of the A–D ring junction.[27] The use of the more potent dicyanovinyl Michael acceptor in lieu of the ethyl acrylate failed to afford an isolable macrocycle (ESI†).

Dihydrodipyrrin with -SMe as a blocking unit. An analogue of dihydrodipyrrin **3** containing a methylthio (**6**) rather than bromo group blocking the 9-pyrrolic position was examined next. The acidic conditions investigated for the condensation of dihydrodipyrrin **22** and **6** included $BF_3{\cdot}OEt_2$, TMSOTf/DTBP, $Bi(OTf)_3$, $Ga(OTf)_3$, $Sc(OTf)_3$, and $Yb(OTf)_3$ (all in CH_2Cl_2, except $BF_3{\cdot}OEt_2$ in CH_3CN). The progress of the reaction was monitored by TLC and by LD-MS. All these conditions failed to afford the expected hydrobilin. Surprisingly, $Yb(OTf)_3$ and $Sc(OTf)_3$ gave the *B*,*D*-tetradehydrocorrin **TDC-4** directly (Scheme 9, right). The effects of the concentration of reagents, equivalents of Lewis acid, solvent, and the presence/absence of proton scavenger (DTBP) were also studied. The use of dilute reactants (1 mM) in CH_2Cl_2 containing $Yb(OTf)_3$ (5 mM) at room temperature for 16 h afforded a 50% isolated yield of **TDC-4**. The methylthio group is believed to be located at the β-pyrrole position of the macrocycle.

The location of the methylthio group at the pyrrole α-position in dihydrodipyrrin **6** – expected on the basis of the synthesis from known pyrrole **16** – was confirmed by the strong coupling signal between the two neighboring β-pyrrolic protons in the COSY spectrum (see the ESI†). ESI-MS analysis of **TDC-4** showed a molecular ion peak (m/z = 509.2733) consistent with the molecular formula $C_{32}H_{36}N_4S$ (calcd 509.2733 for $M + H^+$). The ^1H NMR spectrum indicated only five peripheral alkenyl protons (five singlets in the range of δ 5.3–6.6 ppm). Absorption spectroscopy and 2-dimensional NMR experiments confirmed the tetradehydrocorrin chromophore. NOESY or COSY experiments did not give any direct evidence concerning the location of the methylthio group on the macrocycle, hence the proposed structure must be regarded as provisional in the absence of a single-crystal X-ray diffraction analysis.

A possible explanation for the formation of β-methylthio-tetradehydrocorrin **TDC-4** is shown in Scheme 10. Condensation of **22** and **6** produces the hydrobilin intermediate **I**, which is likely to assume more of a lockwasher rather than planar conformation owing to the steric bulk of the juxtaposed methyl and methylthio groups across the A–D gap. Further cyclization ensues as shown in **II** to give the A–D ring closure of the corrin analogue **III**. Thiiranium formation gives **IV**, which upon loss of



Scheme 10 Possible mechanism for the methylthio shift and related literature precedent.

the β-proton gives the β-methylthiotetradehydrocorrin **TDC-4**. This proposed mechanism is precedented by arylthio migration from the α- to β-position of pyrrole, as shown in the bottom of Scheme 10. Protonation of α-arylthiopyrrole **II-pyr** affords **III-pyr**, which undergoes thiiranium formation to give **IV-pyr**; subsequent rearrangement gives the β-arylthiopyrrole **V**.[50,51] The rearrangement of **I** leading to **TDC-4** is driven by the reaction of the pyrrole α-position with the electrophilic iminium ion (shown for **II**), whereas the rearrangement of **II-pyr** is driven by an analogous electrophilic process, protonation of the pyrrole α-position. The proposed mechanism suggests calculations to address the relative energies of the intermediates as well as the conformation of the hydrobilin(s).

Concise synthesis of a *B*,*C*-tetradehydrocorrin

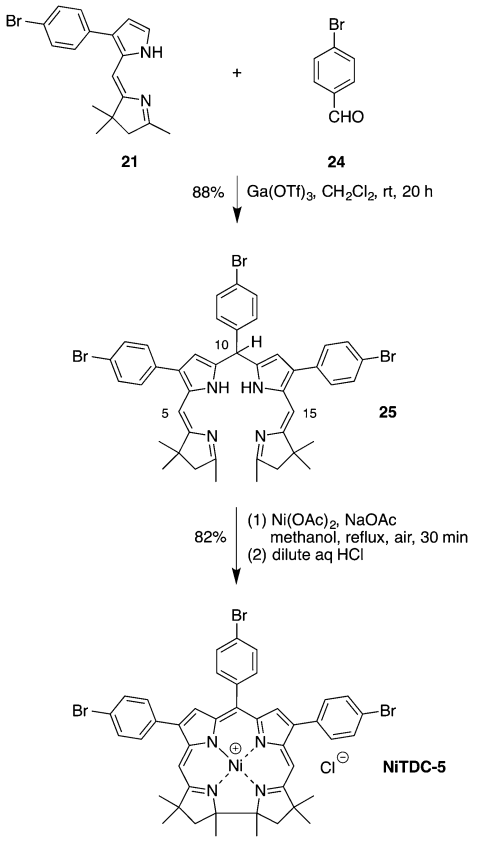
The facile reaction of the pyrrole unit in dihydrodipyrrin **21** with the carboxaldehyde of dihydrodipyrrin **4a** (Scheme 8) prompted examination of a route to a 7,8,12,13-tetradehydrocorrin (Scheme 11). Acid-catalyzed condensation of dihydrodipyrrin **21** and 4-bromobenzaldehyde (**24**) was found to give biladiene **25** in 88% yield. Biladiene **25** underwent facile oxidation during column chromatography or in a solution open to the air. Following a reported method to prepare nickel(II)-octadehydrocorrins,[52,53] treatment of **25** with nickel acetate tetrahydrate and sodium acetate in refluxing methanol for 30 min followed by dilute hydrochloric acid afforded the *B*,*C*-tetradehydrocorrin nickel chloride **NiTDC-5** in 82% yield. A defining feature of the *B*,*C*-tetradehydrocorrin is the presence of two pyrroline rings at the A–D ring junction, *versus* the pyrroline–pyrrole rings at the A–D junction in the prior *B*,*D*-tetradehydrocorrins (**TDC-1–4**).

Characterization

The synthetic studies described above led to 27 new hydrodipyrrins, four new bacteriochlorins, and three new tetradehydrocorrins. The compounds described in the body of the paper were generally characterized by ^{1}H and ^{13}C NMR spectroscopy as well as accurate-mass ESI-MS; the macrocycles were also examined by absorption spectroscopy. In some cases ^{13}C NMR spectra were not obtained due to small quantities, paramagnetic samples (copper bacteriochlorins), or exploratory syntheses that did not lead to fruitful results (*e.g.*, **S1–S8** and others in the ESI†). The four new bacteriochlorins were obtained in minute quantities, the low yields of which were estimated by absorption spectroscopy. The tetradehydrocorrins, on the other hand, were obtained in sufficient quantities for yields to be determined by isolation, and the compounds were examined in detail as described below.

Tetradehydrocorrin **TDC-3** was characterized by ^{1}H and ^{13}C NMR spectroscopy, ESI-MS and absorption spectroscopy. Five peripheral protons resonate in the range of δ 5.4–6.7 ppm. The methylene protons in each pyrroline ring display an AB splitting pattern (δ 2.0–2.5, 2.7 ppm). In addition, two doublets (δ 6.0, 7.4 ppm) can be assigned to the two alkenyl protons in the acrylate substituent. The absorption spectrum (Fig. 1A) shows an intense band at 340 nm, a shoulder at 438 nm and a broad band from 500–900 nm, all of which are characteristic of *B*,*D*-tetradehydrocorrin macrocycles.[18]

TDC-4 exhibits an absorption spectrum (Fig. 1B) with λ_{max} at 318 nm, a weak shoulder at 438 nm, and a weak, broad band from 500–900 nm. The ^{1}H NMR, ^{13}C NMR, gHMQC, and NOESY spectra of **TDC-4** were obtained, and all protons were assigned (see the ESI†). Distinctive features in the ^{1}H NMR spectrum include the following: (1) an AB splitting pattern assigned to the two methylene protons of the pyrroline unit distal from the A–D ring junction; (2) five singlets in the range of δ 5.3–6.6 ppm assigned to the five peripheral alkenyl protons; and (3) two broad peaks in the low-field region assigned to the NH protons.



Scheme 11 Synthesis of a *B,C*-tetradehydrocorrin.

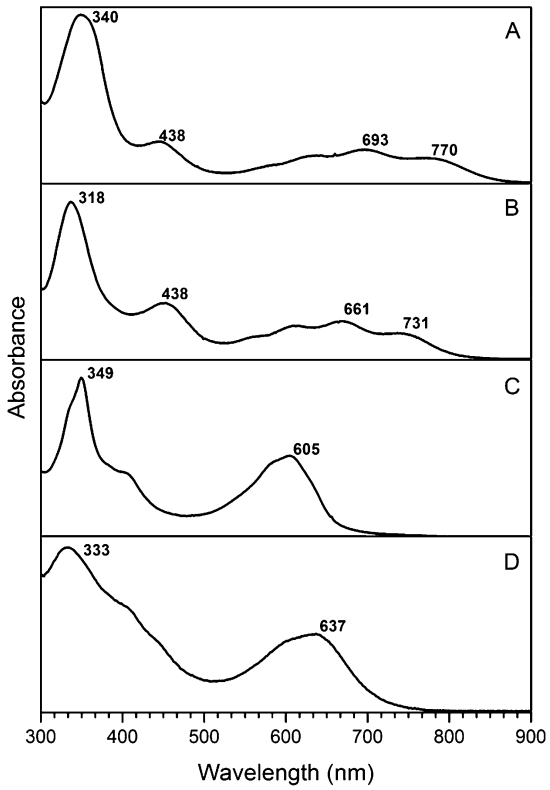


Fig. 1 Absorption spectra of **TDC-3** (A), **TDC-4** (B), **NiTDC-5** (C) and 1,20-dihydrobacteriochlorin **23** (D) in CH_2Cl_2 at room temperature.

The tetradehydrocorrin nickel chloride (**NiTDC-5**) was characterized by ^{1}H and ^{13}C NMR spectroscopy, ESI-MS and absorption spectroscopy. **NiTDC-5** has a C_2 axis (assuming that the 1,19-dimethyl groups are *trans* to one another; if *cis*, there is a plane of symmetry) bisecting the A–D ring junction, hence the two *meso*-protons are identical with each other, and the two β-pyrrolic protons are identical with each other. Two singlets (6.86, 7.30 ppm) observed in the ^{1}H NMR spectrum are assigned to the *meso*-protons and the β-pyrrolic protons, respectively. An AB splitting pattern, assigned to the two methylene protons of both pyrroline units, was also observed (δ 2.44, 2.64 ppm). A high-resolution mass spectrum showed an intense molecular ion with loss of chloride (or other apical ion) at *m*/*z* 904.9973, with the expected isotopic pattern for nickel. The absorption spectrum showed an intense absorption at 349 nm and a broad band from 500–700 nm with λ_{max} at 605 nm (Fig. 1C).

The unusual structure **23** (1,20-dihydrobacteriochlorin) exhibits an absorption spectrum (Fig. 1D) that is consistent with the absorption of a similar metal-free 1,20-dihydroporphyrin reported by Smith *et al.*[54,55]

The indium bacteriochlorins **InBC-1** and **InBC-2** were characterized by ^{1}H NMR spectroscopy, LD-MS, ESI-MS, absorption spectroscopy, and fluorescence spectroscopy. Because both macrocycles are unsymmetrically substituted, each peripheral proton resonates uniquely (an apparent singlet) in the range of δ 8.5–10.0 ppm. In addition, the two gem-dimethyl groups give rise to four singlets, and the CH_2 group in each pyrroline ring gives rise to a pair of doublets in the range of δ 4.4–4.7 ppm. Mass spectrometric analysis in each case gave the molecular ion peak as well as a peak consistent with loss of chloride. The absorption and fluorescence spectra of **InBC-1** and **InBC-2** in toluene are shown in Fig. 2, with the respective $Q_y(0,0)$ absorption band at 773 and 765 nm, and the $Q_y(0,0)$ fluorescence maximum at 789 and 775 nm.

The copper bacteriochlorins **CuBC-3** and **CuBC-4** were characterized by LD-MS, ESI-MS, and absorption spectroscopy. ^{1}H NMR spectroscopy typically is not applicable for copper(II) bacteriochlorins. Fluorescence is not expected (and none was found) in these two cases. The absorption spectra of **CuBC-3** and **CuBC-4** in toluene are shown in Fig. 2, with the $Q_y(0,0)$ band at 744 and 711 nm, respectively. The absorption spectrum of **CuBC-4** showed typical features of an oxobacteriochlorin, including (1) a hypsochromic shift of the Q_y band, and (2) a bathochromic shift and apparent hypochromic effect in the B_y band.[56]

The spectral data including the position, intensity, and full-width at half-maximum (fwhm) of the long-wavelength absorption band and emission band; and intensity ratios of the Q_y to B band are listed in Table 1. The spectral data of indium(III)bacteriochlorins (**InBC-5** and **InBC-6**) are also listed as benchmarks (Chart 2).[43] Comparison of these spectral data leads to some interesting findings: (1) the wavelengths of the Q_y bands are in the following order: **InBC-6** (782 nm) > **InBC-1** (773 nm) > **InBC-2** (765 nm) ~ **InBC-5** (763 nm), indicating that an unsymmetrically substituted bacteriochlorin can finely tune the position of

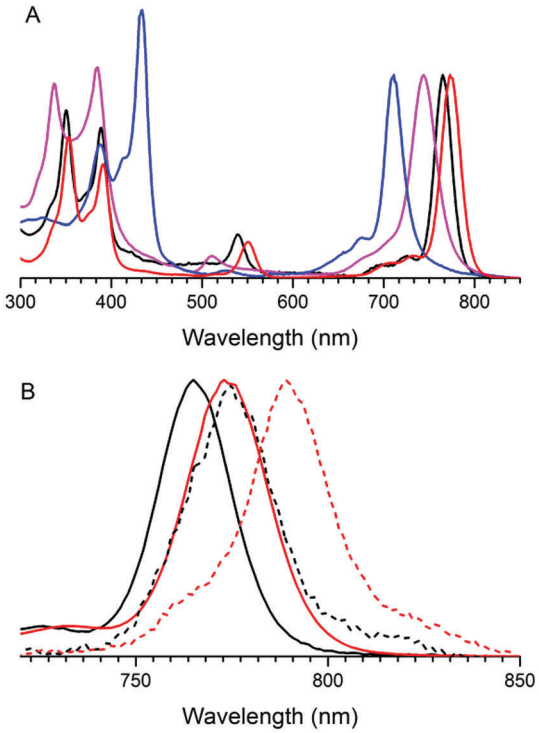


Fig. 2 Absorption spectra (A) and fluorescence spectra (B) of bacteriochlorins in toluene at room temperature (normalized at the Q_y band). The labels and colors in the graph are as follows: **InBC-1** (red trace), **InBC-2** (black trace), **CuBC-3** (magenta trace) and **CuBC-4** (blue trace). The emission spectra are drawn in dashed lines.

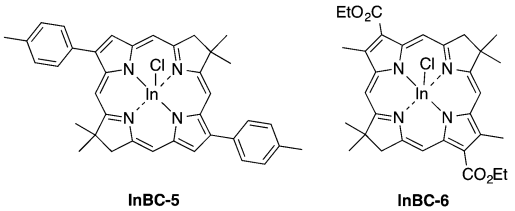


Chart 2 Benchmark bacteriochlorins.

the Q_y band with narrow bandwidth (fwhm ~20 nm). (2) The Stokes shift is in the following order: **InBC-1** (263 cm^{-1}) > **InBC-2** (169 cm^{-1}) > **InBC-5** (103 cm^{-1}) ~ **InBC-6** (49 cm^{-1}). The larger Stokes shift of unsymmetrically substituted bacteriochlorins, compared with those of symmetrically substituted ones, indicates more substantial structure changes upon photoexcitation.

Outlook

A significant advance in routes to tetradehydrocorrins (*B*,*C*- and *B*,*D*-types) has been achieved, yet the objective of the research – gaining access to unsymmetrically substituted bacteriochlorins – remains challenging. Herein, 18 new target hydrodipyrrins equipped with various entities at the α-pyrrole or α-pyrroline position and various degrees of saturation (dihydro, tetrahydro, hexahydro) have been prepared as building blocks for use in studies of macrocycle formation. Among these, 10 hydrodipyrrins (1 tetrahydrodipyrrin and 9 dihydrodipyrrins) with α-pyrrole (H, methylthio, bromo, methyl, and ethoxycarbonyl) or α-pyrroline (methyl, formyl, dimethoxymethyl, and iminomethyl) substituents have afforded reactions leading to a bacteriochlorin or tetradehydrocorrin. Unsymmetrically substituted bacteriochlorins were prepared by the use of dihydrodipyrrins bearing various α-pyrrolic substituents (H, bromo, methyl, and ethoxycarbonyl). Two *B*,*D*-tetradehydrocorrins were produced by acid-catalyzed condensation using one hydrodipyrrin with a methylthio or bromo group as the blocking unit at the 9-pyrrole site, and a second hydrodipyrrin with a methyl or ethyl acrylate group at the 1-pyrroline position. A *B*,*C*-tetradehydrocorrin was obtained upon condensation of two equivalents of a 1-methyldihydrodipyrrin and an aryl aldehyde. These studies provide insights into the synthetic chemistry of hydrodipyrrins and hydrobilins as well as processes leading to tetrapyrrole macrocycles. While our interests lie strongly toward bacteriochlorins rather than corrin analogues, we note that the synthesis of corrin analogues has been relatively unexplored.[10,12,57] Access to the entire slate of dehydrocorrins (hexadehydro-, tetradehydro-, and didehydrocorrins) ranging from *A*,*B*,*C*,*D*-octadehydrocorrins to corrins themselves would be exceptionally valuable for probing the structural features leading to the emergence of corrin-like properties. A strong motivation for the study of such complexes stems from the growing interest in using earth-abundant metals as catalysts for transformations such as photosynthetic hydrogen evolution.[58]

The origin of the facile formation of tetradehydrocorrins *versus* bacteriochlorins remains unclear. The electrocyclization of an 18π-system has been proposed in the synthesis of

Table 1 Spectral properties of bacteriochlorins[a]

Bacteriochlorins	$B_y(0,0)$[b] abs λ (nm)	$B_x(0,0)$[b] abs λ (nm)	$Q_x(0,0)$ abs λ (nm)	$Q_y(0,0)$ abs λ (nm)	$Q_y(0,0)$ abs fwhm (nm)	$Q_y(0,0)$ em λ (nm)	$Q_y(0,0)$ em fwhm (nm)	Δabs–em (cm^{-1})	I_{Q_y}/I_B[c]
InBC-1	353	391	550	773	25	789	24	263	1.4
InBC-2	350	389	539	765	22	775	25	169	1.2
CuBC-3	337	385	511	744	33	—	—	—	1.0
CuBC-4	388	434	528	711	24	—	—	—	0.76
InBC-5[d]	350	388	539	763	23	769	31	103	1.1
InBC-6[d]	354	395	559	782	21	785	23	49	1.3

[a] In toluene at room temperature. [b] The two Soret features are labeled $B_x(0,0)$ and $B_y(0,0)$, but the bands may be of mixed parentage. [c] Ratio of the peak intensities of the $Q_y(0,0)$ band to the Soret (B) maximum. [d] Data from ref. 42.

isobacteriochlorins and chlorins.[24,59,60] Early studies on the synthesis of vitamin B_{12} proposed a 16π-electrocyclization of a secocorrin-diradical to construct the corrin macrocycle, wherein the diradical was created upon H-atom abstraction.[61] While more recent analysis has prompted a turn away from this mechanism,[62] the tetradehydrocorrins reported herein do not require H-atom abstraction to form the requisite precursor polyene. Scheme 12 shows these two competitive electrocyclization processes, starting from a hydrobilin (assuming M^{2+} as the metal center) to produce a bacteriochlorin or *B*,*D*-tetradehydrocorrin; examples of the latter include **TDC-1** and **TDC-2** (Scheme 3) as well as **TDC-3** and **TDC-4** (Scheme 9). A similar 16π-electrocyclization, with a difference in the location of the double bond, could afford the *B*,*C*-tetradehydrocorrin **NiTDC-5** (Scheme 11). While it has proved tempting over the years to ascribe some hydroporphyrin macrocyclizations to electrocyclization processes, such pathways in the absence of stereochemical evidence or solvent effect studies are mere conceptual guideposts. Moreover, a 16π-electrocyclization is not the only possible pathway leading to the tetradehydrocorrin. In some examples, the tetradehydrocorrin might be produced through a more traditional nucleophile–electrophile reaction (*e.g.*, pyrrole + pyrroline reaction giving **TDC-4** in Schemes 9 and 10, or pyrroline α-carbanion + imine reaction leading to **NiTDC-5** in Scheme 11) activated by the acid catalyst. A number of proposed intermediates and associated mechanisms should be amenable to calculation to gauge their energetics and hence their chemical likelihood.

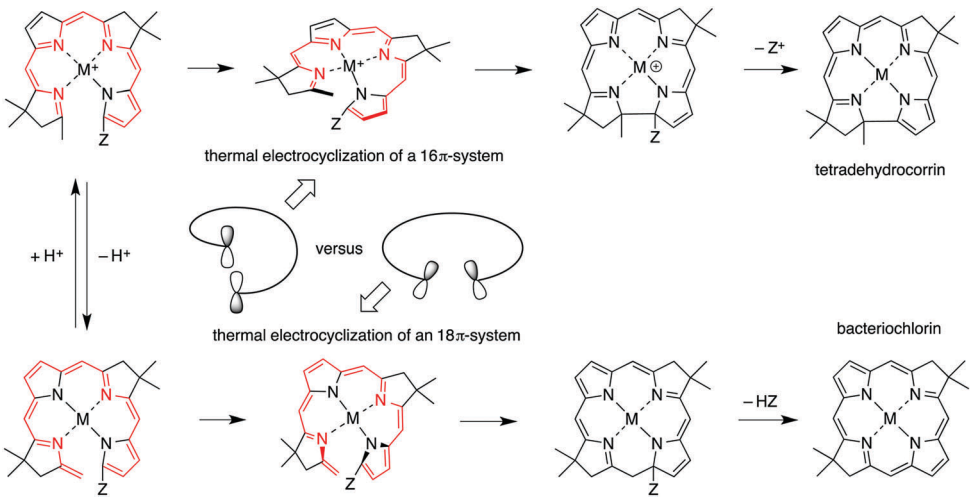
To improve the yields of bacteriochlorins for the reactions reported herein, at least two advances are required: (1) a new approach to join the respective hydrodipyrrins; and (2) a new blocking unit in the hydrobilin. The choice of the blocking/leaving group in the hydrobilin is a key aspect of a successful macrocyclization. Although low yields and small quantities of bacteriochlorin severely limit the present applications in synthetic chemistry, some research opportunities may be available. Examples include (1) incorporation of $^{13}C/^{15}N$ isotopes at one or more specific sites on the π-system of the bacteriochlorin for vibronic studies, (2) preparation and photophysical studies of unsymmetrically substituted dioxobacteriochlorins (analogues of native tolyporphin A), and (3) introduction of distinct substituents (*e.g.* hydrophobic/hydrophilic substituents) on the opposite sides of the macrocycle for self-assembly and photophysical studies.

Experimental section

General methods

^1H NMR and ^{13}C NMR spectra were collected at room temperature in $CDCl_3$ unless noted otherwise. Electrospray ionization mass spectrometry (ESI-MS) data are reported for the molecular ion or protonated molecular ion. Bromination was performed using freshly recrystallized NBS (from water). THF used in all reactions was freshly distilled from Na/benzophenone ketyl. All commercially available materials were used as received. Non-commercial compounds **3**,[26] **5c**,[19] **10**,[20] **11a**,[38] **11b**,[39] **11c**,[19] **12c**,[19] **13b**,[41] **16**,[40] **20**,[20] **21**[23] and **22**[20] (as well as **13c**,[41] **13d**,[63] **S9**,[25] **S12**,[20] **S13**,[19] **S17**,[19] **S19**,[21] **S24**,[25] **S26**,[20] **S32**,[25] **S33**,[25] **S34**,[64] and **S35**;[25] ESI†) were prepared as described in the literature and assessed for purity by ^1H NMR spectroscopy. Estimates of the yields by absorption spectroscopy was carried out using interrogation of the long-wavelength absorption band (Q_y) with ε = 100 000 M^{-1} cm^{-1} for indium bacteriochlorins[43] and ε = 130 000 M^{-1} cm^{-1} for copper bacteriochlorins.[48]

9-Ethoxycarbonyl-1-formyl-2,3-dihydro-3,3,7,8-tetramethyldipyrrin (4a). Following a general procedure,[20] a solution of **15a** (50. mg, 0.18 mmol) in 1,4-dioxane (5.0 mL) was treated with SeO_2 (60. mg, 0.54 mmol) under argon and stirred at room temperature. The progress of the reaction was monitored by absorption spectroscopy. After 30 min, the reaction mixture was diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4) and concentrated. Chromatography [silica, CH_2Cl_2] gave a red-orange solid (32 mg, 59%): ^1H NMR (400 MHz) δ 1.27 (s, 6H), 1.37 (t, J = 7.2 Hz, 3H), 2.09 (s, 3H), 2.28 (s, 3H),



Scheme 12 Possible 16π/18π-electrocyclizations.

2.73 (s, 2H), 4.32 (q, J = 7.2 Hz, 2H), 6.14 (s, 1H), 10.00 (s, 1H), 10.84 (br, 1H); ^{13}C NMR (100 MHz) δ 9.1, 10.4, 14.6, 29.3, 41.2, 46.2, 60.1, 110.8, 121.5, 122.7, 126.8, 130.2, 161.6, 162.7, 170.5, 190.3; ESI-MS obsd 303.1699, calcd 303.1703 [$(M + H)^+$, M = $C_{17}H_{22}N_2O_3$]; λ_{abs} (CH_2Cl_2) 459 nm.

8-Ethoxycarbonyl-1-formyl-2,3-dihydro-3,3,7,9-tetramethyldipyrrin (4b). Following a general procedure,[20] a solution of **15b** (50. mg, 0.18 mmol) in 1,4-dioxane (5.0 mL) was treated with SeO_2 (60. mg, 0.54 mmol) under argon and stirred at room temperature. The progress of the reaction was monitored by absorption spectroscopy. After 15 min, the reaction mixture was diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4) and concentrated. Chromatography [silica, CH_2Cl_2] gave a red-orange solid (36 mg, 66%): ^{1}H NMR (400 MHz) δ 1.25 (s, 6H), 1.37 (t, J = 6.8 Hz, 3H), 2.35 (s, 3H), 2.57 (s, 3H), 2.72 (s, 2H), 4.29 (q, J = 6.8 Hz, 2H), 6.16 (s, 1H), 9.97 (s, 1H), 10.57 (br, 1H); ^{13}C NMR (100 MHz) δ 11.3, 14.6, 14.8, 29.3, 41.1, 45.9, 59.4, 111.2, 112.2, 125.0, 126.4, 139.6, 159.7, 166.0, 168.5, 189.9; ESI-MS obsd 303.1699, calcd 303.1703 [$(M + H)^+$, M = $C_{17}H_{22}N_2O_3$]; λ_{abs} (CH_2Cl_2) 473 nm.

8-Ethoxycarbonyl-1-formyl-2,3-dihydro-3,3-dimethyl-7-*p*-tolyldipyrrin (4c). Following a general procedure,[20] a solution of dihydrodipyrrin **15c** (123 mg, 0.350 mmol) in 1,4-dioxane (7.0 mL) was treated with SeO_2 (117 mg, 1.05 mmol) under argon and stirred at room temperature for 60 min. Ethyl acetate (50 mL) was added, and the mixture was washed with saturated aqueous $NaHCO_3$ solution, water and brine. The organic layer was dried (Na_2SO_4), concentrated and chromatographed [silica, hexanes/ethyl acetate (4 : 1)] to afford a yellow oil (50.1 mg, 39%): ^{1}H NMR (300 MHz) δ 1.17 (s, 6H), 1.21 (t, J = 7.2 Hz, 3H), 2.41 (s, 3H), 2.71 (s, 2H), 4.17 (q, J = 7.2 Hz, 2H), 6.08 (s, 1H), 7.23–7.29 (m, 4H), 7.63 (d, J = 3.0 Hz, 1H), 10.0 (s, 1H), 11.1 (br, 1H); ^{13}C NMR (100 MHz) δ 14.3, 21.4, 29.1, 41.1, 46.1, 59.6, 112.4, 115.2, 127.3, 128.4, 129.4, 130.8, 136.9, 161.7, 164.5, 169.8, 189.9; ESI-MS obsd 365.1860, calcd 365.1860 [$(M + H)^+$, M = $C_{22}H_{24}N_2O_3$]; λ_{abs} (CH_2Cl_2) 451 nm.

1-[(*N*-*tert*-Butyl)iminomethyl]-8-ethoxycarbonyl-2,3-dihydro-3,3-dimethyl-7-*p*-tolyldipyrrin (4c-Im). A solution of **4c** (22 mg, 0.060 mmol) in CH_2Cl_2 (6.0 mL) was treated with *tert*-$BuNH_2$ (25 μL, 0.24 mmol) under argon. The resulting mixture was stirred at room temperature and monitored by absorption spectroscopy. After 2 h, the mixture was concentrated to afford a brownish yellow solid (16 mg, 63%): mp 165–166 °C; ^{1}H NMR (300 MHz) δ 1.16 (s, 6H), 1.20 (t, J = 7.2 Hz, 3H), 1.30 (s, 9H), 2.40 (s, 3H), 2.81 (s, 2H), 4.17 (q, J = 7.2 Hz, 2H), 5.86 (s, 1H), 7.19–7.30 (m, 4H), 7.56 (d, J = 3.0 Hz, 1H), 8.28 (s, 1H), 11.25 (br, 1H); ^{13}C NMR (100 MHz) δ 14.4, 21.4, 21.5, 29.1, 29.6, 40.3, 48.0, 58.9, 59.4, 106.6, 114.7 125.4, 125.8, 128.4, 129.8, 130.8, 131.4, 136.2, 153.5, 162.7, 165.0, 173.9; ESI-MS obsd 420.2658, calcd 420.2645 [$(M + H)^+$, M = $C_{26}H_{33}N_3O_2$]; λ_{abs} (CH_2Cl_2) 406 nm.

9-Ethoxycarbonyl-2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3,7,8-tetramethyldipyrrin (5a). Following a general procedure,[21] a solution of **15a** (104 mg, 0.361 mmol) in 1,4-dioxane (10.0 mL) was treated with SeO_2 (120. mg, 1.08 mmol) under argon and stirred at room temperature. The progress of the reaction was monitored by absorption spectroscopy. After 15 min, the reaction mixture was diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4), concentrated to an orange-red solid (crude **4a**). The residue was dissolved in trimethyl orthoformate (5.0 mL) and then $TsOH{\cdot}H_2O$ (205 mg, 1.08 mmol) was added at room temperature. After 1 h, the reaction mixture was diluted with ethyl acetate and quenched by the addition of saturated aqueous $NaHCO_3$ solution. The separated organic phase was washed with water, dried (Na_2SO_4), concentrated and chromatographed [silica, CH_2Cl_2, then hexane/ethyl acetate (1 : 1)] to afford an orange-yellow oil (80 mg, 64%): ^{1}H NMR (300 MHz) δ 1.23 (s, 6H), 1.37 (t, J = 7.2 Hz, 3H), 2.04 (s, 3H), 2.27 (s, 3H), 2.64 (s, 2H), 3.49 (s, 6H), 4.30 (q, J = 7.2 Hz, 2H), 5.01 (s, 1H), 5.83 (s, 1H), 10.90 (br, 1H); ^{13}C NMR (100 MHz) δ 8.9, 10.5, 14.7, 29.2, 40.6, 48.1, 55.2, 59.7, 103.3, 104.3, 119.1, 119.4, 126.8, 130.8, 161.8, 162.6, 176.1; ESI-MS obsd 349.21218, calcd 349.21128 [$(M + H)^+$, M = $C_{19}H_{28}N_2O_4$].

8-Ethoxycarbonyl-2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3,7,9-tetramethyldipyrrin (5b). Following a general procedure,[21] a solution of **15b** (207 mg, 0.720 mmol) in 1,4-dioxane (15 mL) was treated with SeO_2 (240. mg, 2.16 mmol) and stirred at room temperature. The progress of the reaction was monitored by absorption spectroscopy. After 15 min, the reaction mixture was diluted with ethyl acetate, washed with brine and water, dried and concentrated to give an orange-red solid. The resulting residue (crude **4b**) was dissolved in trimethyl orthoformate (7.2 mL), and $TsOH{\cdot}H_2O$ (415 mg, 2.16 mmol) was added at room temperature under argon. After 1 h, the reaction mixture was diluted with ethyl acetate, washed with water, dried (Na_2SO_4), and concentrated. Column chromatography [silica, hexanes/ethyl acetate (3 : 1)] afforded a yellow oil (130 mg, 52%): ^{1}H NMR (400 MHz) δ 1.22 (s, 6H), 1.35 (t, 3H), 2.30 (s, 3H), 2.53 (s, 3H), 2.62 (s, 2H), 3.47 (s, 6H), 4.27 (q, 2H), 5.02 (s, 1H), 5.84 (s, 1H), 10.7 (br, 1H); ^{13}C NMR (100 MHz) δ 11.1, 14.55, 14.60, 29.2, 40.4, 48.3, 54.6, 59.0, 102.7, 104.4, 111.1, 120.3, 125.9, 136.8, 158.9, 166.4, 173.9; ESI-MS obsd 349.2113, calcd 349.2122 [$(M + H)^+$, M = $C_{19}H_{28}N_2O_4$].

2,3-Dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyl-9-methylthiodipyrrin (6). Following a general procedure,[19] In a first flask, a solution of **19** (2.28 g, 6.63 mmol) in anhydrous THF (50 mL) under argon was treated with NaOMe (1.79 g, 33.1 mmol). The mixture was bubbled with argon for 10 min and stirred for 1 h at room temperature. In a second flask, $TiCl_3$ (20 wt% $TiCl_3$ in 3 wt% HCl, 21 mL, 33 mmol) and water (264 mL) were combined. The solution was bubbled with argon for 10 min, NH_4OAc (51 g, 0.66 mol) was slowly added to buffer the solution to pH 6.0, and then THF (18 mL) was added under argon. After 30 min, the solution in the first flask was transferred *via* a cannula to the solution in the second flask. The resulting mixture was stirred at room temperature for 14 h under argon. Then saturated aqueous $NaHCO_3$ (500 mL) was added. The mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), concentrated and chromatographed [alumina, hexanes/ethyl acetate (3 : 1)] to give a yellow oil (0.28 g, 14%): ^{1}H NMR (300 MHz) δ 1.20 (s, 6H), 2.39 (s, 3H), 2.62 (s, 2H), 3.48 (s, 6H), 5.04 (s, 1H), 5.80 (s, 1H), 6.11 (m, 1H), 6.25 (m, 1H), 10.58 (br, 1H); ^{13}C NMR (100 MHz) δ 21.5, 29.3,

40.3, 48.2, 55.1, 103.1, 107.1, 110.7, 114.8, 123.3, 132.8, 160.5, 174.9; ESI-MS obsd 295.1477, calcd 295.1475 [$(M + H)^+$, M = $C_{15}H_{22}N_2O_2S$].

9-Bromo-1-formyl-2,3-dihydro-7-(4-iodophenyl)-3,3-dimethyldipyrrin (7). Following a general procedure,[26] a solution of **20** (30. mg, 0.074 mmol) in THF (7.4 mL) was treated with NBS (13 mg, 0.074 mmol) in one portion at −78 °C under argon. The reaction mixture was stirred at −78 °C for 1 h. Then hexanes/Et_3N (20 mL, 99 : 1) was added. The dry ice/acetone bath was removed, and water (50 mL) was added. After the mixture warmed to room temperature, ethyl acetate was added. The organic extract was washed (brine and water), dried (Na_2SO_4), concentrated and chromatographed [silica, hexane/CH_2Cl_2 (3 : 1)] to give an orange-red solid (16 mg, 45%): ^{1}H NMR (300 MHz) δ 1.21 (s, 6H), 2.73 (s, 2H), 6.18 (s, 1H), 6.27 (d, J = 3.0 Hz, 1H), 7.11 (d, J = 8.7 Hz, 2H), 7.74 (d, J = 8.7 Hz, 2H), 10.02 (s, 1H), 10.80 (br, 1H); ESI-MS obsd 482.9568, calcd 482.9564 [$(M + H)^+$, M = $C_{18}H_{16}N_2OBrI$]. Note: compound **7** was prone to decomposition upon dissolution in chlorinated solvents and during chromatography on silica, but was stable for weeks upon storage in the solid state at −20 °C.

7-(4-Bromophenyl)-1-(3-ethoxy-3-oxo-prop-1-enyl)-2,3-dihydro-3,3-dimethyldipyrrin (8). A solution of dihydrodipyrrin **21** (100 mg, 0.290 mmol) in 1,4-dioxane (6.0 mL) was treated with SeO_2 (110 mg, 0.991 mmol) at room temperature. The reaction progress was monitored with absorption spectroscopy. After 60 min, the reaction mixture was poured into saturated aqueous $NaHCO_3$ solution. Then ethyl acetate (20 mL) was added. The organic layer was separated, dried (Na_2SO_4) and concentrated. The residue was purified by passage through a short silica column with elution by CH_2Cl_2. The crude aldehyde was dissolved in dry CH_2Cl_2 (6.0 mL) and treated with (ethoxycarbonylmethylene)triphenylphosphorane (100 mg, 0.287 mmol). The reaction mixture was stirred at room temperature for 20 h, and then concentrated to a solid. Chromatography [silica, hexanes/CH_2Cl_2 (1 : 1)] gave a red solid (33 mg, 26%): mp 128–130 °C (dec.); ^{1}H NMR (300 MHz) δ 1.23 (s, 6H), 1.35 (t, J = 6.9 Hz, 3H), 2.69 (s, 2H), 4.28 (q, J = 6.9 Hz, 2H), 6.11 (s, 1H), 6.29 (m, 1H), 6.26 (d, J = 16.2 Hz, 1H), 6.94 (m, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 16.2 Hz, 1H), 10.98 (br, 1H); ^{13}C NMR (75 MHz) δ 14.4, 29.3, 41.2, 48.0, 61.2, 107.6, 109.4, 119.9, 120.7, 127.6, 127.8, 130.3, 131.7, 135.8, 139.2, 162.0, 166.1, 169.9, 200.8; ESI-MS obsd 427.1010, calcd 427.1016 [$(M + H)^+$, M = $C_{22}H_{23}BrN_2O_2$].

2,3,4,5-Tetrahydro-1,3,3-trimethyl-7-*p*-tolyldipyrrin (9). Following a general procedure,[25] a mixture of **10** (22 mg, 0.060 mmol) and NH_4OAc (16 mg, 0.24 mmol) in THF (6.0 mL) was treated with zinc dust (16 mg, 0.24 mmol) under argon. The resulting mixture was stirred at room temperature. After 2 h, ethyl acetate was added, and the mixture was filtered. The filtrate cake was washed with ethyl acetate. The filtrate was washed with water/brine, dried (Na_2SO_4), concentrated and chromatographed (silica, ethyl acetate) to afford a viscous yellow oil (16 mg, 63%): ^{1}H NMR (300 MHz) δ 0.95 (s, 3H), 1.11 (s, 3H), 2.07 (s, 3H), 2.36–2.39 (m, 5H), 2.63 (ABX, ^2J = 15.3 Hz, ^3J = 12.3, 1H), 3.02 (ABX, ^2J = 15.3 Hz, ^3J = 2.4, 1H), 3.70 (AB, J = 11.7 Hz, 1H), 6.31 (t, J = 2.4 Hz, 1H), 6.77 (t, J = 2.4 Hz, 1H), 7.21 (d, J = 8.2 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 10.2 (br, 1H); ^{13}C NMR (75 MHz) δ 20.6, 21.2, 22.9, 26.5, 27.2, 42.0, 54.3, 80.1, 108.1, 116.0 127.8, 128.1, 129.1, 134.4, 134.7, 174.5; ESI-MS obsd 281.2017, calcd 281.2012 [$(M + H)^+$, M = $C_{19}H_{24}N_2$].

2-Ethoxycarbonyl-3,4-dimethyl-5-(2-nitroethyl)pyrrole (12a). Following a general procedure,[19] samples of **11a** (24 g, 0.12 mol), nitromethane (19 mL, 0.36 mol), KOAc (13 g, 0.13 mol) and CH_3NH_2·HCl (8.8 g, 0.13 mol) were stirred in MeOH (150 mL) for 3 h. The mixture was diluted with water (500 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined extract was washed with brine (100 mL), dried and concentrated to give an orange-red solid, which was dissolved in absolute ethanol (500 mL) and treated with $NaBH_4$ (7.5 g, 0.20 mol). After 30 min, the mixture was concentrated. The residue was taken up in water (200 mL), and the solution was acidified with acetic acid to pH ∼5. The mixture was extracted with CH_2Cl_2. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated. Chromatography [silica, hexanes/ethyl acetate (3 : 1)] gave a yellow solid (10.3 g, 36%): mp 118–119 °C; ^{1}H NMR (300 MHz) δ 1.35 (t, J = 7.2 Hz, 3H), 1.95 (s, 3H), 2.24 (s, 3H), 3.28 (t, J = 6.9 Hz, 2H), 4.30 (q, J = 7.2 Hz, 2H), 4.54 (t, J = 7.2 Hz, 2H), 8.80 (br, 1H); ^{13}C NMR (75 MHz) δ 8.9, 10.9, 14.7, 24.4, 60.4, 74.4, 118.6, 118.7, 127.5, 127.6, 162.7; ESI-MS obsd 241.11828, calcd 241.11761 [$(M + H)^+$, M = $C_{11}H_{16}N_2O_4$].

3-Ethoxycarbonyl-2,4-dimethyl-5-(2-nitroethyl)pyrrole (12b). Following a general procedure,[19] samples of **11b** (7.35 g, 37.7 mmol), nitromethane (6.0 mL, 0.11 mol), KOAc (4.44 g, 45.2 mmol) and CH_3NH_2·HCl (3.05 g, 45.2 mmol) were stirred together in MeOH (40 mL) for 6 h. The mixture was diluted with water (300 mL) and extracted with CH_2Cl_2 (100 mL × 3). The combined extract was washed with brine (100 mL), dried and concentrated to give an orange-red solid, which was dissolved in absolute ethanol (200 mL) and treated with $NaBH_4$ (2.83 g, 75.4 mmol). After 30 min, the mixture was concentrated. The residue was taken up in water (200 mL), and the solution was acidified with acetic acid. The mixture was extracted with CH_2Cl_2. The extract was washed with water and brine, dried (Na_2SO_4), concentrated and chromatographed [silica, hexanes/ethyl acetate (1 : 1)] to give a yellow solid (5.72 g, 63%): mp 127–129 °C; ^{1}H NMR (300 MHz) δ 1.34 (t, J = 7.2 Hz, 3H), 2.17 (s, 3H), 2.44 (s, 3H), 3.20 (t, J = 6.9 Hz, 2H), 4.27 (q, J = 7.2 Hz, 2H), 4.50 (t, J = 6.6 Hz, 2H), 8.35 (br, 1H); ^{13}C NMR (100 MHz) δ 10.9, 14.0, 14.5, 23.3, 59.3, 75.0, 111.2, 118.4, 120.6, 135.4, 166.5; ESI-MS obsd 241.11762, calcd 241.11828 [$(M + H)^+$, M = $C_{11}H_{16}N_2O_4$].

6-(5-Ethoxycarbonyl-3,4-dimethylpyrrol-2-yl)-4,4-dimethyl-5-nitrohexan-2-one (14a). Following a general procedure,[20] a mixture of **12a** (6.69 g, 27.9 mmol) and **13a** (8.23 g, 84.0 mmol) was treated with DBU (12.5 mL, 84.0 mmol) at room temperature. After 16 h, the reaction mixture was diluted with ethyl acetate and washed with aqueous HCl (0.5 M), saturated aqueous $NaHCO_3$ solution, and then brine. The organic layer was dried (Na_2SO_4) and filtered. The filtrate was concentrated. The resulting residue was chromatographed (silica, CH_2Cl_2) to give a pale-yellow solid (3.70 g, 44%): mp 130–131 °C; ^{1}H NMR (300 MHz) δ 1.13 (s, 3H), 1.27 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H),

1.92 (s, 3H), 2.15 (s, 3H), 2.21 (s, 3H), 2.50 (AB, ^2J = 17.4 Hz, 2H), 2.98 (ABX, ^2J = 15.3 Hz, ^3J = 2.4 Hz, 1H), 3.27 (ABX, ^2J = 15.3 Hz, ^3J = 11.7 Hz, 1H), 4.27 (q, J = 7.2 Hz, 2H), 5.12 (ABX, ^2J = 11.7 Hz, ^3J = 2.4 Hz, 1H), 8.65 (br, 1H); ^{13}C NMR (100 MHz) δ 8.9, 10.7, 14.7, 24.2, 24.6, 25.2, 32.0, 37.0, 51.5, 60.1, 93.6, 118.5, 118.6, 127.1, 127.5, 161.8, 207.0; ESI-MS obsd 339.19145, calcd 339.19091 [(M + H)$^+$, M = $C_{17}H_{26}N_2O_5$].

6-(4-Ethoxycarbonyl-3,5-dimethylpyrrol-2-yl)-4,4-dimethyl-5-nitrohexan-2-one (14b). Following a general procedure,[20] a mixture of **12b** (5.72 g, 23.8 mmol) and **13a** (7.00 g, 71.4 mmol) was treated with DBU (10.7 mL, 71.4 mmol) at room temperature. After 16 h, the reaction mixture was diluted with ethyl acetate and washed with brine and water (200 mL × 3). The organic layer was dried, filtered, concentrated and chromatographed [silica, hexanes/ethyl acetate (1 : 1)] to give a yellow oil (6.08 g, 75%): ^{1}H NMR (300 MHz) δ 1.12 (s, 3H), 1.24 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H), 2.15 (s, 6H), 2.40 (s, 3H), 2.50 (AB, ^2J = 17.4 Hz, 2H), 2.94 (ABX, ^2J = 15.3 Hz, ^3J = 2.4 Hz, 1H), 3.22 (ABX, ^2J = 15.3 Hz, ^3J = 11.4 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 5.05 (ABX, ^2J = 11.4 Hz, ^3J = 2.4 Hz, 1H), 8.26 (br, 1H); ^{13}C NMR (100 MHz) δ 10.7, 13.8, 14.4, 23.9, 24.0, 24.2, 31.7, 36.6, 51.1, 59.0, 94.1, 110.8, 118.3, 120.5, 135.3, 166.3, 207.3; ESI-MS obsd 339.19178, calcd 339.19145 [(M + H)$^+$, M = $C_{17}H_{26}N_2O_5$].

6-(4-Ethoxycarbonyl-3-*p*-tolylpyrrol-2-yl)-4,4-dimethyl-5-nitrohexa-2-one (14c). Following a general procedure,[20] a mixture of **12c** (1.81 g, 6.00 mmol) and **13a** (0.820 mL, 7.20 mmol) was treated with DBU (2.70 mL, 18.0 mmol) at room temperature. The reaction mixture became dark and was stirred for 16 h at room temperature. Ethyl acetate (100 mL) was added. The mixture was washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography [silica, hexanes/ethyl acetate (3 : 2)] afforded a light yellow solid (1.22 g, 51%): mp 150–152 °C; ^{1}H NMR (300 MHz) δ 0.99 (s, 3H), 1.03 (s, 3H), 1.16 (t, J = 7.2 Hz, 3H), 2.04 (s, 3H), 2.36 (s, 3H), 2.27, 2.45 (AB, J = 17.7 Hz, 2H), 2.95 (ABX, ^2J = 15.6 Hz, ^3J = 2.4 Hz, 1H), 3.19 (ABX, ^2J = 15.6 Hz, ^3J = 11.4 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 4.97 (ABX, ^2J = 11.4, ^3J = 2.4 Hz, 1H), 7.13–7.17 (m, 4H), 7.31 (d, J = 3.0 Hz, 1H), 8.65 (br, 1H); ^{13}C NMR (100 MHz) δ 14.4, 21.5, 23.9, 24.2, 24.9, 31.8, 37.0, 51.2, 59.6, 94.9, 115.2, 124.1, 124.7, 125.2, 128.7, 130.4, 131.5, 136.5, 164.8, 206.8; ESI-MS obsd 401.2085, calcd 401.2071 [(M + H)$^+$, M = $C_{22}H_{28}N_2O_5$].

9-Ethoxycarbonyl-2,3-dihydro-1,3,3,7,8-pentamethyldipyrrin (15a). Following a general procedure,[20] in a first flask, a solution of **14a** (3.70 g, 10.9 mmol) in THF/methanol (10 : 1, 20 mL) under argon was treated with NaOMe (1.78 g, 33.0 mmol). The mixture was stirred at room temperature for 50 min. In a second flask, NH_4OAc (41 g, 0.54 mol) in distilled THF (140 mL) was bubbled with argon for 15 min. Then $TiCl_3$ (20 wt% in 3 wt% HCl solution, 56 mL, 87 mmol) was added, and the mixture was degassed by bubbling argon for another 30 min. Then, the first flask mixture was transferred *via* cannula to the buffered $TiCl_3$ solution. The resulting mixture was stirred at room temperature for 16 h under argon. The mixture was then filtered through a pad of Celite, and the filtered material was washed with ethyl acetate. The eluent was washed with saturated aqueous $NaHCO_3$, then brine and water. The organic layer was dried, filtered and concentrated. Chromatography (silica, CH_2Cl_2) afforded a light yellow solid (1.02 g, 32%): mp 116–118 °C; ^{1}H NMR (300 MHz) δ 1.21 (s, 6H), 1.37 (t, J = 6.9 Hz, 3H), 2.03 (s, 3H), 2.24 (s, 3H), 2.27 (s, 3H), 2.52 (s, 2H), 4.29 (q, J = 6.9 Hz, 2H), 5.68 (s, 1H), 11.16 (br, 1H); ^{13}C NMR (75 MHz) δ 8.9, 10.5, 14.6, 21.0, 29.2, 41.5, 53.9, 59.5, 101.2, 118.4, 126.8, 131.3, 161.8, 163.9, 178.7; ESI-MS obsd 289.19105, calcd 289.19081 [(M + H)$^+$, M = $C_{17}H_{24}N_2O_2$].

8-Ethoxycarbonyl-2,3-dihydro-1,3,3,7,9-pentamethyldipyrrin (15b). Following a general procedure,[20] a solution of **14b** (6.08 g, 18.0 mmol) in THF/methanol (10 : 1, 20 mL) under argon was treated with NaOMe (2.92 g, 54.0 mmol). The mixture was stirred at room temperature for 50 min. In a second flask, NH_4OAc (68 g, 0.88 mol) in distilled THF/water (150 mL/50 mL) was bubbled with argon for 30 min. Then $TiCl_3$ (20 wt% in 3 wt% HCl solution, 93 mL, 0.14 mol) was added, the mixture was degassed by bubbling argon for another 30 min. Then, the first flask mixture was transferred *via* cannula to the buffered $TiCl_3$ solution. The resulting mixture was stirred at room temperature for 16 h under argon. The mixture was then filtered through a pad of Celite, washed with ethyl acetate. The eluent was washed with saturated aqueous $NaHCO_3$, then brine and water. The organic layer was dried, filtered and concentrated. Column chromatography (silica, CH_2Cl_2) afforded a light yellow solid (3.32 g, 59%): mp 98–99 °C; ^{1}H NMR (300 MHz) δ 1.20 (s, 6H), 1.35 (t, J = 7.2 Hz, 3H), 2.20 (s, 3H), 2.29 (s, 3H), 2.49 (s, 2H), 2.53 (s, 3H), 4.26 (q, J = 7.2 Hz, 2H), 5.68 (s, 1H), 10.88 (br, 1H); ^{13}C NMR (100 MHz) δ 11.2, 14.7, 14.8, 20.9, 29.4, 41.4, 53.9, 59.1, 101.5, 111.0, 119.0, 126.4, 136.4, 160.4, 166.8, 176.5; ESI-MS obsd 289.19102, calcd 289.19105 [(M + H)$^+$, M = $C_{17}H_{24}N_2O_2$].

8-Ethoxycarbonyl-2,3-dihydro-1,3,3-trimethyl-7-*p*-tolyldipyrrin (15c). Following a general procedure,[20] in a first flask, a solution of **14c** (1.20 g, 3.00 mmol) in freshly distilled THF (30.0 mL) was treated with NaOMe (825 mg, 15.0 mmol). The reaction mixture was stirred and degassed by bubbling argon through the solution for 45 min. In a second flask purged with argon, $TiCl_3$ (20 wt% in 2N HCl solution, 21 mL, 33 mmol) and 120 mL of H_2O were combined under argon, and the mixture was degassed by bubbling argon for 10 min. Then, NH_4OAc (92.4 g, 1.20 mol) was slowly added under argon bubbling to buffer the mixture to pH 6.0. The mixture was further bubbled with argon for 30 min. The mixture in the first flask was transferred *via* cannula to the buffered $TiCl_3$ mixture. The resulting mixture was stirred at room temperature for 16 h under argon. Then saturated aqueous $NaHCO_3$ (250 mL) was added. The mixture was filtered over a pad of Celite and eluted with ethyl acetate. The filtrate was washed with water and brine. The organic layer was dried (Na_2SO_4), concentrated and chromatographed [silica, hexanes/ethyl acetate (9 : 1)] to afford a yellow solid (422 mg, 40%): mp 83–85 °C; ^{1}H NMR (300 MHz) δ 1.13 (s, 6H), 1.21 (t, J = 7.2 Hz, 3H), 2.23 (s, 3H), 2.40 (s, 3H), 2.51 (s, 2H), 4.17 (q, J = 7.2 Hz, 2H), 5.67 (s, 1H), 7.19–7.30 (m, 4H), 7.51 (d, J = 2.7 Hz, 1H), 11.4 (br, 1H); ^{13}C NMR (100 MHz) δ 14.3, 20.7, 21.3, 29.0, 41.2, 53.8, 59.2, 102.2, 114.2, 123.4, 124.7, 128.2, 129.9, 130.8, 131.8, 135.7, 162.5, 165.0, 177.7; ESI-MS obsd 351.2075, calcd 351.2067 [(M + H)$^+$, M = $C_{22}H_{26}N_2O_2$]; λ_{abs} (CH_2Cl_2) 330 nm.

2-Formyl-5-methylthiopyrrole (17). Following a general procedure,[19] a solution of **16** (7.1 g, 63 mmol) in CH_2Cl_2 (120 mL) and DMF (7.1 mL, 94 mL) was treated dropwise with $POCl_3$ (8.7 mL, 94 mmol) under argon at 0 °C. After 1 h, the ice bath was removed, and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred for 20 h before being cooled to 0 °C again, whereupon 2.0 M NaOH (50 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic extract was washed (brine), dried (Na_2SO_4), concentrated and chromatographed [silica, CH_2Cl_2/ethyl acetate (9 : 1)] to afford a dark red solid (4.5 g, 51%): mp 96–98 °C; ^{1}H NMR (300 MHz) δ 2.52 (s, 3H), 6.28 (m, 1H), 6.96 (m, 1H), 9.36 (s, 1H), 10.98 (br, 1H); ^{13}C NMR (75 Hz) δ 17.7, 112.9, 123.6, 133.9, 136.9, 178.1; ESI-MS obsd 142.0323, calcd 142.0321 [$(M + H)^+$, M = C_6H_7NOS].

2-(2-Nitroethyl)-5-methylthiopyrrole (18). Following a general procedure,[19] a solution of **17** (4.70 g, 33.3 mmol), potassium acetate (3.91 g, 40.0 mmol) and methylamine hydrochloride (2.75 g, 40.0 mmol) in absolute ethanol (40 mL) was treated with nitromethane (5.5 mL, 100 mmol). The mixture was stirred for 4 h and monitored by TLC analysis [silica, CH_2Cl_2/ethyl acetate (3 : 1)]. Then, water was added. The mixture was extracted with CH_2Cl_2. The organic phase was dried and concentrated to give a red solid. The crude solid was dissolved in a mixture of $CHCl_3$ (75 mL) and 2-propanol (24 mL), to which silica (23 g) was then added. The mixture was stirred vigorously, and $NaBH_4$ (1.90 g, 50.0 mmol) was added in several batches. After 1 h, the mixture was filtered. The filter cake was washed with CH_2Cl_2. The filtrate was concentrated and chromatographed (silica, CH_2Cl_2) to afford an orange-red oil (2.59 g, 42%): ^{1}H NMR (300 MHz) δ 2.32 (s, 3H), 3.28 (t, J = 6.6 Hz 2H), 4.59 (t, J = 6.6 Hz, 2H), 5.97 (m, 1H), 6.25 (m, 1H), 8.16 (br, 1H); ^{13}C NMR (100 MHz) δ 21.6, 25.6, 75.0, 108.5, 115.5, 121.4, 128.4; ESI-MS obsd 187.0541, calcd 187.0536 [$(M + H)^+$, M = $C_7H_{10}N_2O_2S$].

1,1-Dimethoxy-4,4-dimethyl-5-nitro-6-(5-methylthiopyrrol-2-yl)hexan-2-one (19). Following a general procedure,[19] a mixture of **18** (2.59 g, 13.9 mmol) and **13b** (4.39 g, 27.8 mmol) was treated with DBU (4.3 mL, 28 mmol) at room temperature. After 16 h, the reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried (Na_2SO_4), concentrated and chromatographed [silica, hexanes/ethyl acetate (3 : 1)] to give a red oil (2.28 g, 48%): ^{1}H NMR (300 MHz) δ 1.14 (s, 3H), 1.22 (s, 3H), 2.29 (s, 3H), 2.65 (AB, ^2J = 18.9 Hz, 2H), 2.98 (ABX, ^2J = 15.6 Hz, ^3J = 2.4 Hz, 1H), 3.32 (ABX, ^2J = 15.6 Hz, ^3J = 12.0 Hz, 1H), 3.43 (s, 3H), 3.44 (s, 3H), 4.37 (s, 1H), 5.14 (ABX, ^2J = 12.0 Hz, ^3J = 2.4 Hz, 1H), 5.93 (m, 1H), 6.20 (m, 1H), 8.10 (br, 1H); ^{13}C NMR (100 MHz) δ 21.8, 24.3, 24.4, 27.0, 36.6, 45.1, 55.4, 94.5, 104.9, 109.1, 115.7, 121.4, 128.6, 203.7; ESI-MS obsd 345.1473, calcd 345.1479 [$(M + H)^+$, M = $C_{15}H_{24}N_2O_5S$].

10-[7-(4-Bromophenyl)-2,3-dihydro-1,3,3-trimethyldipyrrin-9-yl]-13-(4-bromophenyl)-1-ethoxycarbonyl-2,3,7,7,17,17-hexamethyl-1,20-dihydrobacteriochlorin (23). A mixture of **21** (24 mg, 0.079 mmol) and **4a** (54 mg, 0.16 mmol) in dry CH_2Cl_2 (8.0 mL) was treated with $Ga(OTf)_3$ (123 mg, 0.24 mmol) and stirred under argon at room temperature for 20 h. The mixture was diluted with CH_2Cl_2, washed with brine thoroughly, dried (Na_2SO_4) and concentrated. The resulting residue was dissolved in methanol (8.0 mL) and refluxed for 5 h exposed to air. The solution quickly turned green. Then the solution was concentrated. The residue was dissolved in CH_2Cl_2, washed with brine and water, dried (Na_2SO_4) and concentrated. Chromatography [silica, hexanes/ethyl acetate (4 : 1)] afforded a green solid (2.2 mg, 2.8%): ^{1}H NMR (300 MHz) δ 1.02 (t, J = 6.9 Hz, 3H), 1.14 (s, 3H), 1.18 (s, 3H), 1.26 (s, 3H), 1.31 (s, 3H), 1.32 (s, 3H), 1.34 (s, 3H), 1.60 (s, 3H), 1.89 (s, 2H), 2.08 (s, 3H), 2.30 (s, 3H), 2.48 (s, 2H), 2.55 (AB, J = 18 Hz, 1H), 2.90 (AB, J = 18 Hz, 1H), 3.10 (AB, J = 18 Hz, 2H), 4.07 (m, 2H), 4.88 (s, 1H), 5.71 (s, 1H), 5.90 (s, 1H), 6.34 (d, J = 3.0 Hz, 1H), 6.87 (s, 1H), 7.19–7.24 (m, 4H), 7.45–7.50 (m, 4H), 10.53 (br, 1H), 11.15 (br, 1H), 12.67 (br, 1H); ESI-MS obsd 966.2793, calcd 966.2826 [M^+, M = $C_{53}H_{56}Br_2N_6O_2$]; λ_{abs} (CH_2Cl_2) 333, 637 nm.

7,10,13-Tris(4-bromophenyl)-2,3,17,18-tetrahydro-1,3,3,17,17,19-hexamethylbiladiene-*ac* (25). A solution of 4-bromobenzaldehyde (**24**, 5.3 mg, 0.029 mmol) and dihydrodipyrrin **21** (20. mg, 0.058 mmol) in CH_2Cl_2 (3.0 mL) was treated with $Ga(OTf)_3$ (45 mg, 0.087 mmol) and stirred at room temperature for 20 h. Saturated aqueous $NaHCO_3$ solution was added, whereupon the mixture was extracted with CH_2Cl_2. The combined organic extract was combined, washed with brine, dried (Na_2SO_4) and concentrated to a magenta solid (22 mg, 88%), which was characterized and used in the next step without further purification: ^{1}H NMR (300 MHz) δ 1.14 (s, 12H), 1.98 (s, 6H), 2.44 (s, 4H), 5.51 (s, 1H), 5.84 (s, 2H), 6.09 (d, J = 3.0 Hz, 2H), 7.27–7.31 (m, 6H), 7.44–7.50 (m, 6H), 10.93 (br, 2H); ^{13}C NMR (75 MHz) δ 20.6, 29.2, 41.3, 44.1, 53.8, 102.2, 107.6, 119.1, 120.9, 122.6, 126.9, 130.0, 130.7, 131.5, 131.8, 133.0, 136.3, 141.3, 161.7, 177.1. The compound was easily oxidized and gave m/z of the corresponding oxidized product (–2H): ESI-MS obsd 849.0779, calcd 849.0798 [$(M + H)^+$, M = $C_{43}H_{39}Br_3N_4$].

Chloroindium(III)-13-ethoxycarbonyl-8,8,18,18-tetramethyl-2,12-di-*p*-tolylbacteriochlorin (InBC-1)

Method A. A solution of dihydrodipyrrins **22** (7.0 mg, 0.025 mmol) and **5c** (10. mg, 0.025 mmol) in CH_2Cl_2 (2.5 mL) was treated with $Bi(OTf)_3$ (33 mg, 0.050 mmol). After stirring for 20 min at room temperature, the reaction mixture was quenched by the addition of Et_3N (0.06 mmol, 8 μL) and then concentrated. The resulting crude product was dissolved in CH_2Cl_2 (2.5 mL), and the stock solution was distributed among five microvials. The solution in each vial was concentrated to a solid. The resulting solids were dissolved in the indicated solvent. Then each solution was treated with $InCl_3$ (11 mg, 0.050 mmol) and TMPi (9 μL, 0.05 mmol) and each reaction mixture was stirred at the indicated temperature. The progress of each microreaction was monitored by absorption spectroscopy. After 1.5 h, each microreaction mixture was diluted with CH_2Cl_2. Water was added to each microvial, and the organic extract was separated, washed with brine, dried (Na_2SO_4), concentrated and chromatographed [silica, CH_2Cl_2/ethyl acetate (4 : 1)] to give the indium bacteriochlorin. The bacteriochlorin yields were determined spectroscopically (Table S1, ESI†). The highest yield was obtained for the reaction carried out in toluene (8%, estimated by absorption spectroscopy at 773 nm, ε assumed[43] = 100 000 M^{-1} cm^{-1}).

Method B. A solution of **4c-Im** (25 mg, 0.060 mmol) and **9** (17 mg, 0.060 mmol) in CH_2Cl_2 (6.0 mL) was treated with $Bi(OTf)_3$ (79 mg, 0.12 mmol). After stirring for 15 min at room temperature, the reaction mixture was quenched by the addition of TMPi (0.10 mL, 0.60 mmol) and then concentrated to a brown solid. The residue was dissolved in toluene (6.0 mL) and treated with $InCl_3$ (133 mg, 0.60 mmol) and TMPi (0.10 mL, 0.60 mmol). The reaction mixture was stirred at 80 °C. Absorption spectroscopy of the reaction mixture showed the formation of the indium bacteriochlorin. After 2 h, the reaction mixture was diluted with ethyl acetate (50 mL). The organic extract was washed with brine and water, dried (Na_2SO_4), concentrated and chromatographed [silica, hexanes/ethyl acetate (3 : 2 to 1 : 1)] to afford **InBC-1** as a pink solid (1 mg, 2%): ^{1}H NMR (400 MHz) δ 1.28 (t, J = 7.2 Hz, 3H), 1.76 (s, 3H), 1.78 (s, 3H), 1.94 (s, 3H), 2.06 (s, 3H), 2.60 (s, 6H), 4.31–4.61 (m, 6H), 7.47 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H), 7.99 (d, J = 8.0 Hz, 2H), 8.43 (s, 1H), 8.62 (s, 1H), 8.67 (s, 1H), 8.69 (s, 1H), 9.68 (s, 1H); MALDI-MS found 769.8; ESI-MS obsd 769.1810, calcd 769.1806 [$(M - H)^-$, M = $C_{41}H_{40}ClInN_4O_2$]; ESI-MS obsd 735.2175, calcd 735.2185 [$(M - Cl)^+$, M = $C_{41}H_{40}ClInN_4O_2$]; λ_{abs} (toluene) 353, 391, 550, 773 nm; λ_{em} (λ_{exe} = 550 nm) 789 nm.

Chloroindium(III)-12-(4-iodophenyl)-8,8,18,18-tetramethyl-2-*p*-tolylbacteriochlorin (InBC-2). A solution of **9** (3.1 mg, 0.011 mmol) and **7** (5.3 mg, 0.011 mmol) in CH_2Cl_2 (1.1 mL) was treated with $TsOH{\cdot}H_2O$ (10. mg, 0.055 mmol). After stirring for 50 min at room temperature, the reaction mixture was quenched by the addition of TMPi (19 μL, 0.11 mmol) and then concentrated. The resulting residue was dissolved in toluene (1.1 mL) and treated with $InCl_3$ (24 mg, 0.11 mmol) and TMPi (19 μL, 0.11 mmol). The reaction mixture was stirred at 90 °C. The reaction progress was monitored by absorption spectroscopy. After 2 h, the reaction mixture was diluted with ethyl acetate. The organic extract was washed with brine and water, dried (Na_2SO_4), concentrated and chromatographed [silica, CH_2Cl_2 then CH_2Cl_2/ethyl acetate (4 : 1)] to afford a pink solid (1%, estimated by absorption spectroscopy at 765 nm, ε assumed[43] = 100 000 M^{-1} cm^{-1}): ^{1}H NMR (400 MHz) δ 1.82 (s, 3H), 1.84 (s, 3H), 2.07 (s, 3H), 2.08 (s, 3H), 2.60 (s, 3H), 4.43 (AB, ^2J = 16.8 Hz, ^3J = 4.4 Hz, 2H), 4.64 (AB, ^2J = 18.0 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 8.4 Hz, 2H), 8.08 (d, J = 8.4 Hz, 2H), 8.73 (s, 1H), 8.75 (s, 1H), 8.77 (m, 2H), 8.78 (s, 1H), 8.82 (s, 1H); MALDI-MS obsd 812.4; ESI-MS obsd 810.0476, calcd 810.0472 [M^+, M = $C_{37}H_{33}ClIInN_4$]; obsd 775.0780, calcd 775.0783 [$(M - Cl)^+$, M = $C_{37}H_{33}ClIInN_4$]; λ_{abs} (toluene) 350, 389, 539, 765 nm; λ_{em} (λ_{exe} = 539 nm) 775 nm.

Copper(II)-2-(4-bromophenyl)-8,8,12,13,18,18-hexamethylbacteriochlorin (CuBC-3). A mixture of dihydrodipyrrin-acetal **5a** (20. mg, 0.057 mmol) and dihydrodipyrrin **21** (20. mg, 0.057 mmol) in CH_2Cl_2 (6 mL) was treated with $Cu(OTf)_2$ (50 mg, 0.14 mmol) at room temperature under argon for 90 min. Then saturated aqueous $NaHCO_3$ solution was added to the reaction mixture, which was then extracted with CH_2Cl_2. The combined organic extract was washed with brine and water, dried (Na_2SO_4) and concentrated to a red-purple gum with the following characterization data: MALDI-MS obsd 689.2; ESI-MS obsd 688.1469, calcd 688.1462 [M^+, M = $C_{35}H_{38}BrCuN_4O_2$]; λ_{abs} (CH_2Cl_2) 540 nm. The residue was dissolved in ethylene glycol (6.0 mL) and treated with powdered NaOH (228 mg, 5.70 mmol). The mixture was degassed by bubbling with argon, then heated to 160 °C under argon, and stirred for 1 h. The mixture was allowed to cool to room temperature, then diluted with ethyl acetate (100 mL) and washed thoroughly with brine and water. The resulting organic phase was dried (Na_2SO_4), concentrated and chromatographed [silica, hexanes/CH_2Cl_2 (1 : 1)] to give a green solid (2% yield, estimated by absorption spectroscopy at 744 nm, ε assumed[48] = 130 000 M^{-1} cm^{-1}): MALDI-MS obsd 612.9; ESI-MS obsd 613.1012, calcd 613.1022 [M^+, M = $C_{32}H_{31}BrCuN_4$]; λ_{abs} (toluene) 337, 385, 511, 744 nm.

Copper(II)-2-(4-bromophenyl)-13-ethoxycarbonyl-8,8,12,18,18-pentamethyl-7,17-dioxobacteriochlorin (CuBC-4). A mixture of dihydrodipyrrin-acetal **5b** (20. mg, 0.057 mmol) and dihydrodipyrrin **21** (20. mg, 0.057 mmol) in CH_2Cl_2 (6 mL) was treated with $Cu(OTf)_2$ (25 mg, 0.068 mmol) at room temperature under argon for 90 min. Then saturated aqueous $NaHCO_3$ solution was added to the reaction mixture, which was then extracted with CH_2Cl_2. The combined organic extract was washed with brine and water, dried (Na_2SO_4) and concentrated to a red-purple solid with the following characterization data: MALDI-MS obsd 689.2; ESI-MS obsd 688.1444, calcd 688.1469 [M^+, M = $C_{35}H_{38}BrCuN_4O_2$]; λ_{abs} (CH_2Cl_2) ~ 550 nm. The residue was dissolved in DMF (10 mL) and treated with anhydrous $CuCl_2$ (115 mg, 0.858 mmol). The mixture was degassed by bubbling argon for 10 min and then heated to 120 °C for 20 h under argon. The mixture was allowed to cool to room temperature and then diluted with ethyl acetate (100 mL) and washed thoroughly with water (4 × 100 mL). The organic phase was dried (Na_2SO_4), concentrated and chromatographed [silica, hexanes/ethyl acetate (4 : 1 then 3 : 1)] to give a green solid (2% yield, estimated by absorption spectroscopy at 711 nm, ε assumed[48] = 130 000 M^{-1} cm^{-1}): MALDI-MS obsd 700.1; ESI-MS obsd 718.0836, calcd 718.0846 [$(M + H_3O)^+$, M = $C_{34}H_{29}BrCuN_4O_4$]; λ_{abs} (toluene) 388, 434, 528, 711 nm.

7-(4-Bromophenyl)-1-(3-ethoxy-3-oxo-prop-1-enyl)-7,8,17,18-tetradehydro-3,3,13,13-tetramethyl-17-*p*-tolylcorrin (TDC-3). A solution of **3** (33 mg, 0.079 mmol) and **8** (33 mg, 0.077 mmol) in CH_2Cl_2 (7.7 mL) was treated with $Ga(OTf)_3$ (120 mg, 0.235 mmol) at room temperature under argon. After 2 h, TLC analysis indicated the completion of the reaction. Saturated aqueous $NaHCO_3$ solution was added. The organic extract was dried (Na_2SO_4) and concentrated. Chromatography [silica, CH_2Cl_2/hexanes (1 : 1)] gave a green solid (12 mg, 21%): ^{1}H NMR (400 MHz) δ 1.23–1.26 (m, 15H), 1.97 (d, J = 12.8 Hz, 1H), 2.38 (s, 3H), 2.46 (d, J = 12.8 Hz, 1H), 2.67–2.78 (AB, J = 17.6 Hz, 2H), 4.12 (q, J = 6.8 Hz, 2H), 5.43 (s, 1H), 5.58 (s, 1H), 6.00 (d, J = 15.2 Hz, 1H), 6.09 (s, 1H), 6.23 (d, J = 3.2 Hz, 1H), 6.68 (d, J = 1.6 Hz, 1H), 7.19–7.23 (m, 3H), 7.37–7.42 (m, 5H), 7.62 (d, J = 8.4 Hz, 1H), 11.43 (br, 1H), 11.99 (br, 1H); ^{13}C NMR (75 MHz) δ 14.4, 21.3, 25.9, 28.1, 29.0, 30.0, 40.7, 48.9, 49.3, 52.3, 60.5, 73.7, 92.5, 97.0, 102.5, 103.0, 116.4, 122.0, 123.1, 126.0, 128.0, 129.4, 130.2, 131.9, 132.2, 134.4, 135.0, 142.2, 142.4, 147.9, 149.7, 152.9, 164.1, 167.0, 170.1, 181.8, 200.9; LD-MS obsd 701.2, calcd

701.2 [$(M + H)^+$]; ESI-MS obsd 700.2388, calcd 700.2407 [(M^+), M = $C_{41}H_{41}BrN_4O_2$]; λ_{abs} (CH_2Cl_2) 340, 438, 693 (br) nm.

7,8,17,18-Tetradehydro-1,3,3,13,13-pentamethyl-7-*p*-tolyl-18-methylthiocorrin (TDC-4). A solution of **22** (11 mg, 0.040 mmol) and **6** (12 mg, 0.040 mmol) in CH_2Cl_2 (40 mL) was treated with $Yb(OTf)_3$ (124 mg, 0.200 mmol) under argon at room temperature and stirred for 3 h. Then, saturated aqueous $NaHCO_3$ solution (50 mL) was added. The organic extract was washed with brine and water, dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (3 : 1)] to give a dark green solid (10.1 mg, 50%): ^{1}H NMR (400 MHz) δ 1.05 (s, 3H), 1.23 (s, 3H), 1.27 (s, 3H), 1.40 (s, 3H), 1.67 (s, 3H), 2.00 (d, J = 12.8 Hz, 1H), 2.33 (s, 3H), 2.43 (s, 3H), 2.51 (d, J = 12.8 Hz, 1H), 2.69 (d, J = 17.6 Hz, 1H), 2.76 (d, J = 17.6 Hz, 1H), 5.54 (s, 1H), 5.56 (s, 1H), 5.80 (s, 1H), 6.14 (m, 1H), 6.85 (m, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 10.88 (br, 1H), 11.61 (br, 1H); ^{13}C NMR (100 MHz) δ 21.6, 21.9, 27.3, 29.0, 29.3, 29.9, 30.0, 40.6, 49.4, 49.9, 52.4, 72.1, 94.1, 95.6, 102.2, 106.8, 110.4, 127.1, 128.6, 129.8, 130.3, 139.0, 143.7, 148.3, 148.5, 149.4, 163.6, 170.5, 179.7; ESI-MS obsd 509.2732, calcd 509.2733 [$(M + H)^+$, M = $C_{32}H_{36}N_4S$]; λ_{abs} (CH_2Cl_2) 318, 438, 661 (br) nm.

7,10,13-Tris(4-bromophenyl)-7,8,12,13-tetradehydro-1,3,3,17,17,19-hexamethylcorrinatonickel(II) chloride (NiTDC-5). Biladiene **25** (22 mg, 0.026 mmol), nickel acetate tetrahydrate (30. mg, 0.12 mmol) and sodium acetate (30. mg, 0.36 mmol) were dissolved in methanol (3.0 mL) and heated to reflux for 30 min. The solution quickly turned to an indigo color. The resulting solution was concentrated, poured into water and extracted with CH_2Cl_2. The combined extract was dried (Na_2SO_4), concentrated to dryness, and chromatographed on alumina. The column was eluted with CH_2Cl_2 until the eluate was colorless and then with methanol/CH_2Cl_2 (1 : 10). The indigo-colored fraction was collected, shaken with aq HCl solution (20 mL, 0.5 M), dried (Na_2SO_4) and concentrated. The residue was crystallized (CH_2Cl_2/hexanes) as dark blue needles (20 mg, 82%): ^{1}H NMR (700 MHz) δ 1.56 (s, 12H), 1.63 (s, 6H), 2.44 (AB, J = 10.4 Hz, 2H), 2.64 (AB, J = 10.4 Hz, 2H), 6.86 (s, 2H), 7.30 (s, 2H), 7.42 (m, 6H), 7.71 (m, 6H); ^{13}C NMR (175 MHz) δ 29.0, 29.2, 29.8, 32.1, 44.6, 51.9, 85.1, 103.6, 123.6, 124.3, 130.7, 131.2, 131.9, 132.3, 132.6, 133.8, 134.7, 148.9, 154.9, 156.4, 173.3; MALDI-MS obsd 905.5; ESI-MS obsd 904.9973, calcd 904.9995 [M^+, M = $C_{43}H_{38}Br_3N_4Ni$]; λ_{abs} (CH_2Cl_2) 349, 601 nm.

Screening method for Scheme 7A. For n microreactions a solution of **5c** (0.005n mmol) and **22** (0.005n mmol) in anhydrous CH_2Cl_2 (n mL) was treated with 2 molar equiv. of $Bi(OTf)_3$. After 20 min the reaction mixture was neutralized with TMPi (2.2 molar equiv.) and concentrated to a solid. The crude solid was dissolved in 0.5n mL of CH_3CN, and the bulk solution was distributed among the n reaction microvials (0.5 mL each) with a 0.005 mmol theoretical amount of linear putative intermediate in each vial. Then TMPi (10 molar equiv.) and a metal salt (10 molar equiv.) were added, and the microreaction contents were stirred at reflux. Reactions were monitored by absorption spectroscopy assuming ε = 100 000 M^{-1} cm^{-1} [50 μL of the sample from the reaction mixture was added to 0.9 mL of toluene/ethanol (3 : 1)], and by LD-MS analysis with 4 time points (30 min, 1 h, 2 h and overnight).

Conflicts of interest

There are no conflicts to declare.

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