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Synthesis of model bacteriochlorophylls containing substituents of native rings A, C and E†

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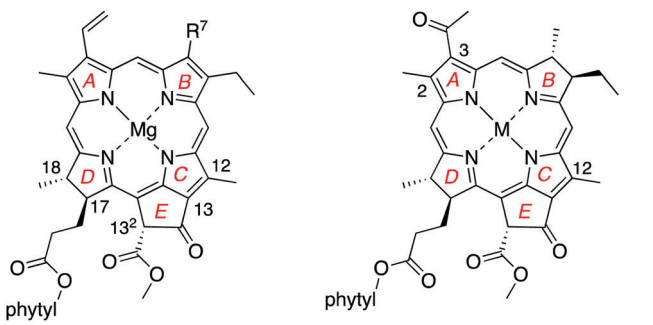
A route under development for the synthesis of bacteriochlorophyll *a* and analogues relies on joining an AD-dihydrodipyrrin (bearing a D-ring carboxaldehyde) and a BC-dihydrodipyrrin (bearing a C-ring β-ketoester group and a B-ring dimethoxymethyl group) *via* Knoevenagel condensation followed by double-ring closure (Nazarov cyclization, electrophilic aromatic substitution, and elimination of methanol). Prior synthetic studies afforded the bacteriochlorophyll skeleton containing a gem-dimethyl group in ring B, a *trans*-dialkyl group in ring D, and a carboethoxy group at the 3-position of ring A. To explore the incorporation of native substituents, the synthesis of two bacteriochlorophyll analogues thereof was pursued, one with 12-methyl and 3-carboethoxy groups and the other with 2,12-dimethyl and 3-acetyl groups. The 12-methyl group resulted in half the yield (*versus* the unsubstituted analogue) in the Knoevenagel reaction, but insignificant effects in all other steps including the rate and yield of double-ring closure despite the known effects of alkyl groups to facilitate electrophilic substitution of pyrroles. The 2-methyl-3-acetyl group, however, resulted in diminished yields in several steps, including the Knoevenagel reaction, but not the double-ring closure. The results point to obstacles and openings on the path to total syntheses of the native pigments.

Introduction

Photosynthetic tetrapyrroles include diverse pigments ranging from the well-known chlorophylls *a* and *b*, the lesser known but still important bacteriochlorophyll *a*, and a broad collection of minor pigments.[1] Bacteriochlorophyll *a* is the chief pigment of anoxygenic photosynthetic bacteria, which rely on a single reaction center *versus* two in tandem (Z scheme with photosystems I and II) for chlorophyll-based, oxygenic photosynthesis, the province of cyanobacteria, plants, and algae. The structures of bacteriochlorophyll *a* and chlorophyll *a* are shown in Chart 1. Bacteriochlorophyll *a* contains the bacteriochlorin (*trans*-tetrahydroporphyrin) chromophore whereas chlorophyll *a* contains the chlorin (dihydroporphyrin) chromophore. It is somewhat paradoxical that anoxygenic photosynthesis is simpler organizationally than plant photosynthesis yet employs architecturally more complex pigments.

We are working to develop rational syntheses of the family of photosynthetic tetrapyrroles, which have been largely neglected as synthetic targets.[2] The strategy under investigation relies on a convergent joining of two dihydrodipyrrins, an AD-half and a BC-half. The route was first developed with a gem-dimethyl group in each pyrroline unit of the respective AD and BC-halves,[3] then extended to accommodate a *trans*-dialkyl group in ring D while retaining a gem-dimethyl group in ring B (Scheme 1).[4] The latter work validated the ability to install stereodefined groups at an early stage of the synthesis (leading to AD half **1a**[4]) and carry such groups through all steps including Knoevenagel condensation with BC half **2a** to form



Chlorophyll *a*, R^7 = Me
Chlorophyll *b*, R^7 = CHO

Bacteriochlorophyll *a*, M = Mg
Bacteriopheophytin *a*, M = H, H

Chart 1 Major photosynthetic tetrapyrrole macrocycles.

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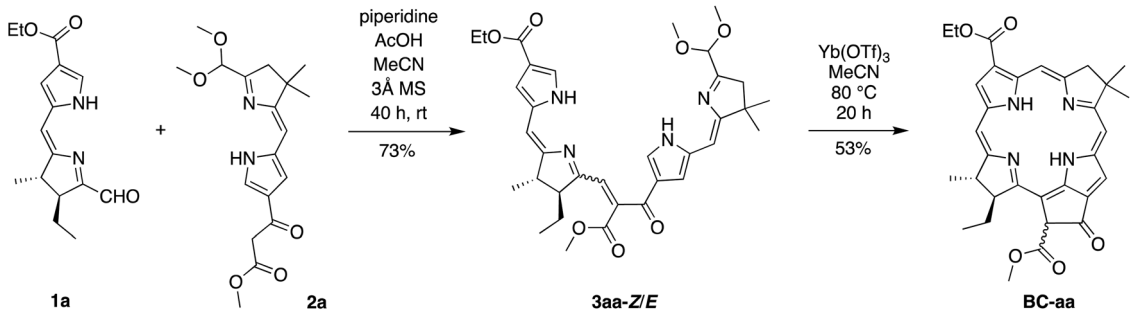
† Electronic supplementary information (ESI) available: Chromatography information; ^{1}H and ^{13}C NMR spectra for all new compounds; and single-crystal X-ray data. CCDC 2083658 (**7**), 2083659 (**8**), 2083662 (**10**), 2083661 (**11**), and 2083660 (**15**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1nj02469h



Scheme 1 Route to bacteriochlorophyll model compounds.

the enone **3aa**-*Z*/*E*, which subsequently undergoes double-ring closure to give the bacteriochlorophyll macrocycle **BC-aa**. The double-ring closure entails Nazarov cyclization, electrophilic aromatic substitution (S_EAr), and elimination of methanol in a one-flask process. The Knoevenagel and double-ring closure transformations afforded good isolated yields (73%, 53%). The *trans*-dialkyl-substituted pyrroline ring is susceptible not only to epimerization but also to adventitious dehydrogenation, which forms the dipyrromethane from the dihydrodipyrrin, yielding the chlorin rather than the bacteriochlorin. The presence of the gem-dimethyl group precludes such dehydrogenation,[5] which in the model study enabled focus on a single *trans*-dialkyl ring rather than two as in native bacteriochlorophylls.

A recent study focused on refined reaction conditions for the double-ring closure using the enone **3aa**.[6] The following findings emerged: (1) the optimal conditions employ the enone **3aa**-*Z*/*E* (0.2 mM) and $Yb(OTf)_3$ (2.0 mM) in acetonitrile at 80 °C; (2) the reaction at 80 °C is half-complete in 43 min and can be terminated after 4 h; (3) both *E* and *Z* enones react comparably, consistent with isomerization under the reaction conditions; and (4) the extent of adventitious dehydrogenation (yielding the corresponding chlorin) is 0.16% (and not detectable in the isolated product).[6] The choice of $Yb(OTf)_3$ as catalyst to support the double-ring closure emerged from screens of diverse acids.[3,6] The findings highlight the robustness of the conditions for accommodating a *trans*-dialkyl-substituted dihydrodipyrrin precursor to give the corresponding bacteriochlorophyll skeleton.

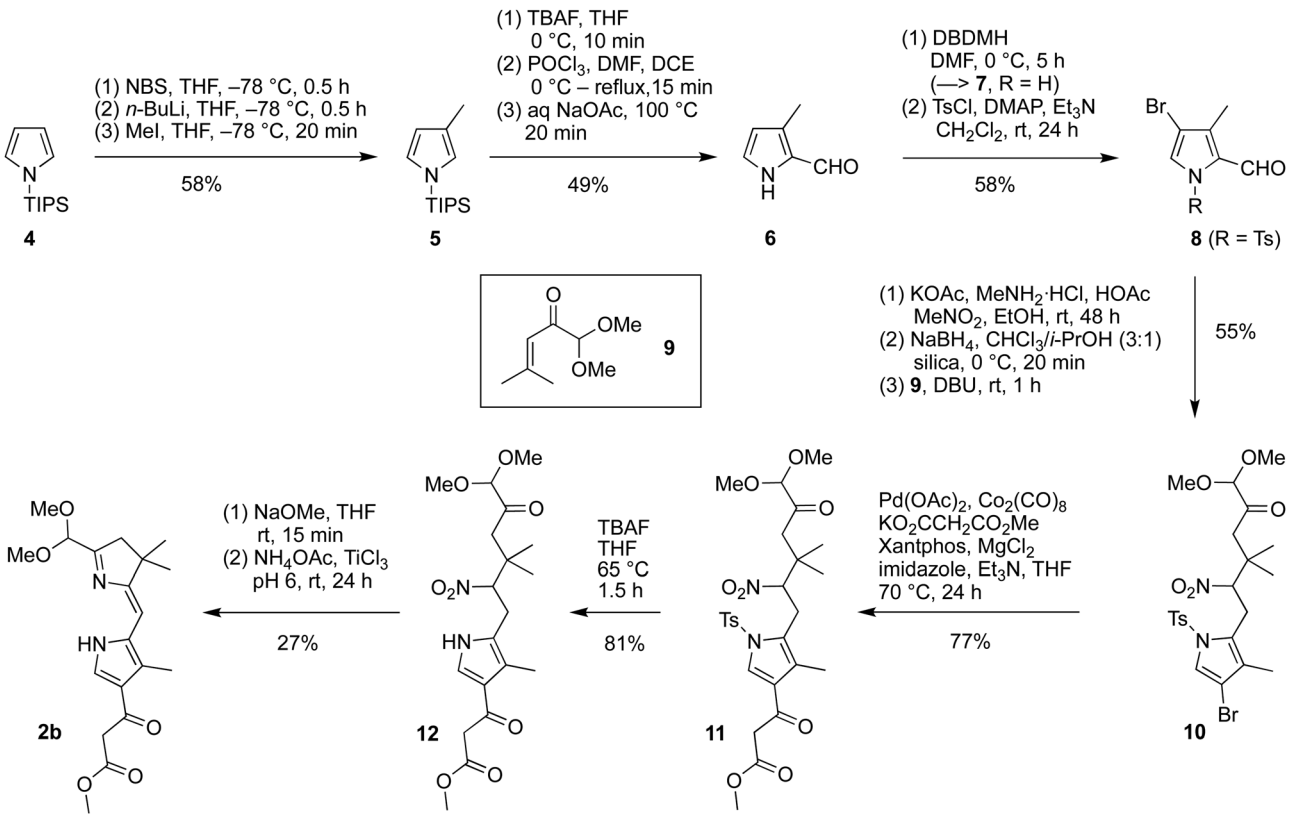
The studies to date have included substituents convenient for model reactions. Such substituents include the 3-carboethoxy group and no substituents at the 2- and 12-positions. Native bacteriochlorophyll *a* bears 3-acetyl and 2,12-dimethyl groups. While the presence or absence of a methyl group may be inconsequential in many instances, appending one methyl group to a pyrrole causes a substantial increase in basicity (by 45-fold)[7] and in the rate of electrophilic substitution (by ~10–30 fold,[8] or 8–170-fold[7]). Moreover, the acetyl group can participate in condensations and oxidations that are not available with the carboethoxy group, which was used previously. Here we report studies aimed at exploring the compatibility of such substituents with the reaction conditions encountered following installation in early-stage precursors. The present work thus addresses the extent to which seemingly innocuous substituents of the native photosynthetic pigments can be introduced in early precursors and conveyed with fidelity to the intact macrocycles.

Results and discussion

Synthesis of a methyl-substituted BC-dihydrodipyrrin

The synthesis of the BC half bearing a ring C methyl substituent is shown in Scheme 2. TIPS-pyrrole (**4**) was treated to a known process[9] to form 3-methyl-TIPS-pyrrole (**5**). Compound **5** was isolated along with a small quantity of unreacted **4** (12 : 1 ratio) and taken forward in the synthesis. Deprotection with TBAF gave an unstable intermediate, which upon Vilsmeier–Haack formylation[10] gave 3-methylpyrrole-2-carboxaldehyde (**6**) as a pale-yellow solid. Bromination of **6** was carried out using the potent reagent 1,3-dibromo-5,5-dimethylhydantoin (DBDMH)[11–13] to give known[13–15] **7** followed by tosylation[16] to obtain the known[15] tosyl-protected bromopyrrole **8** as a pale white crystalline solid. The intermediate 4-bromo-3-methylpyrrole-2-carboxaldehyde (**7**), which was obtained without purification following bromination, was confirmed by ^{1}H NMR spectroscopy and single-crystal X-ray crystallography. Compounds **5–8** are known;[9,13–15] however, the procedures employed here have been improved in the following ways: (1) bromination with DBDMH instead of NBS; and (2) streamlined conversion of **6** to **8**.

Nitro-aldol (Henry) condensation of **8** gave the nitrovinylpyrrole, which upon $NaBH_4$ reduction followed by Michael addition with 1,1-dimethoxy-4-methylpent-3-en-2-one (**9**[17]) gave the nitrohexanone–pyrrole **10**. This route has an antecedent in the synthetic approach developed by Battersby and coworkers 40 years ago toward the natural product bonellin,[18,19] which contains a geminal-dimethyl group in the pyrroline ring.[5] Compound **10**[15] also is known and was prepared here in a streamlined manner without purification of the products of Henry condensation and $NaBH_4$ reduction. The direct carbonylation[3] of **10** with $Co_2(CO)_8$ and methyl potassium malonate in the presence of palladium(II) acetate, Xantphos, $MgCl_2$, imidazole, and triethylamine installed the β-ketoester to form **11**. TLC analysis indicated that most of the starting material was consumed in 24 h, whereas a similar reaction proceeded in up to 48 h.[3] Removal of the tosyl group of **11** by treatment with TBAF (1 M in THF) delivered **12** in 81% yield. McMurry-type ring closure using NaOMe and $TiCl_3$ gave



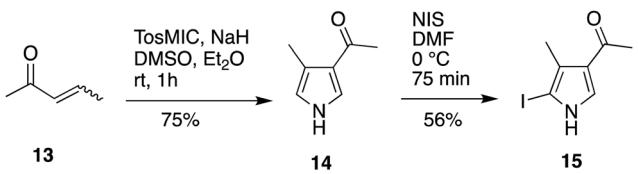
Scheme 2 Synthesis of a methyl-substituted BC dihydrodipyrrin.

dihydrodipyrrin–acetal **2b** in 27% yield, a yield that is typical for such transformations.[15,20] A single-crystal X-ray structure was obtained for compounds **7**, **8**, **10**, and **11**.

Synthesis of an acetyl-substituted AD-dihydrodipyrrin

The synthesis of the ring A pyrrole is shown in Scheme 3. The van Leusen reaction[21] of *E*/*Z*-4-oxo-2-pentene (**13**) with TosMIC gave known[9] 3-acetyl-4-methylpyrrole (**14**) in 75% yield. The reaction was carried out at ~4-fold increased scale *versus* the known synthesis. Subsequent iodination with NIS regioselectively gave 4-acetyl-2-iodo-3-methylpyrrole (**15**) without the generation of unwanted polyiodinated products that often occur with pyrroles.[22] A single-crystal X-ray structure of **15** was obtained, verifying the depicted structure.

The synthesis of the AD half containing the pyrrole acetyl substituent is shown in Scheme 4. The general strategy for forming the AD half follows a route first proposed by Jacobi and coworkers[23] and has been implemented to prepare **1a** with validation of the stereochemistry of the *trans*-dialkyl group in the pyrroline ring.[4] The Sonogashira reaction of 2-iodopyrrole **15** and pentynoic acid **16**[4] afforded the lactone–pyrrole **17**. The latter was then reacted with the Petasis reagent to give the ene–lactone–pyrrole **18**. Subsequent ring-opening in acid followed by a Paal–Knorr-like reaction with ammonium acetate gave the desired dihydrodipyrrin **19**. Finally, the 1-methyl group of **19** was converted to the carboxaldehyde (**1b**) *via* Riley oxidation[24] albeit in low yield. The low yields of the Petasis methenylation and Riley oxidation may arise from competing reaction at the acetyl group of the pyrrole, although acylpyrroles are known to exhibit vinylogous amide behavior[25,26] and are regarded as less reactive than typical carbonyl groups.[27]

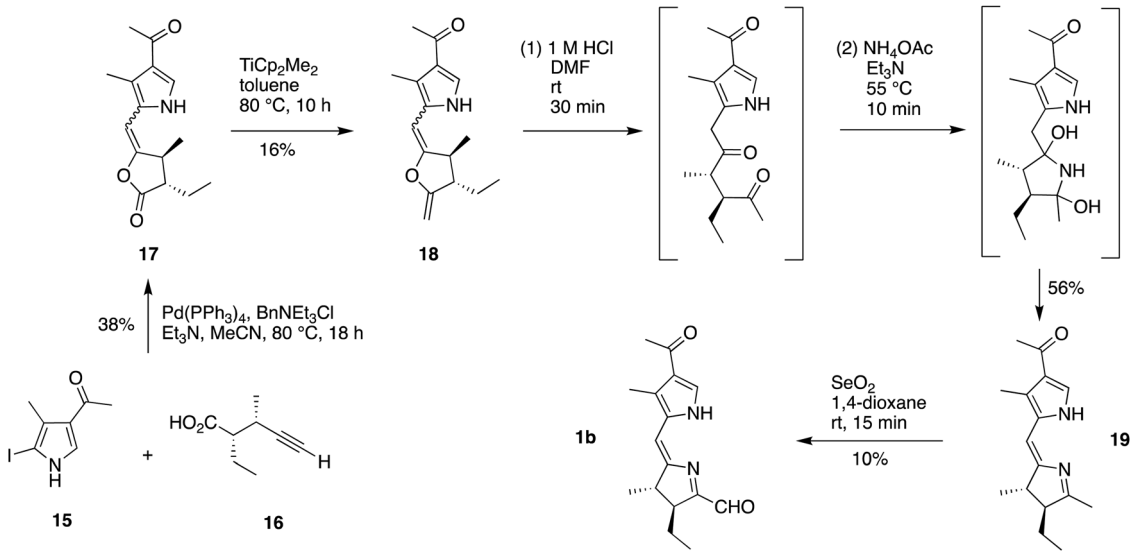


Scheme 3 Synthesis of pyrrole ring A.

Knoevenagel condensation

The Knoevenagel reaction between dihydrodipyrrin **1a** or **1b** (an AD-half) and dihydrodipyrrin **2b** (BC-half) is shown in Scheme 5. The prior synthesis entailed reaction of **1a** and **2a** to give enone **3aa** in 73% yield (70% *E* isomer, 3% *Z* isomer).[4] Similar reaction here of **1a** and **2b** gave enone **3ab**, albeit in 34% yield. Although only one enone isomer was observed, the configuration about the double bond could not be determined by NOESY analysis. While the *E* isomer is often formed preponderantly in Knoevenagel reactions of heteroaromatic β-keto esters, interconversion of the *E* and *Z* isomers occurs during the course of the Nazarov cyclization.[4,28]

In a similar manner, the Knoevenagel reaction of AD-half **1b** and BC-half **2b** gave enone **3bb** in 10% yield after 20 h, again as



Scheme 4 Synthesis of an AD dihydrodipyrrin.

one isomer. An unknown side product with m/z = 667.3344 ($[M + H]^+$ peak determined by accurate mass analysis) was also isolated in a significant amount (1.6 mg compared to 2.0 mg of the desired product) upon purification by column chromatography. By comparison, the product **3bb** has m/z = 617.3344 ($[M + H]^+$). The absorption spectrum (λ_{abs} = 488 nm) of the unknown side product resembled that of enone **3bb** (ESI†).

The low yields in the Knoevenagel reaction[29–31] leading to **3ab** and **3bb** were unexpected and indicate that additional work will be required to develop improved reaction conditions. The Knoevenagel enones are obtained as dark red solids and give orange-red solutions (~0.1 mM). The absorption spectrum of **3ab** or **3bb** in toluene showed a peak maximum in the visible region at 454 nm or 485 nm, respectively. The spectra are shown in Fig. 1.

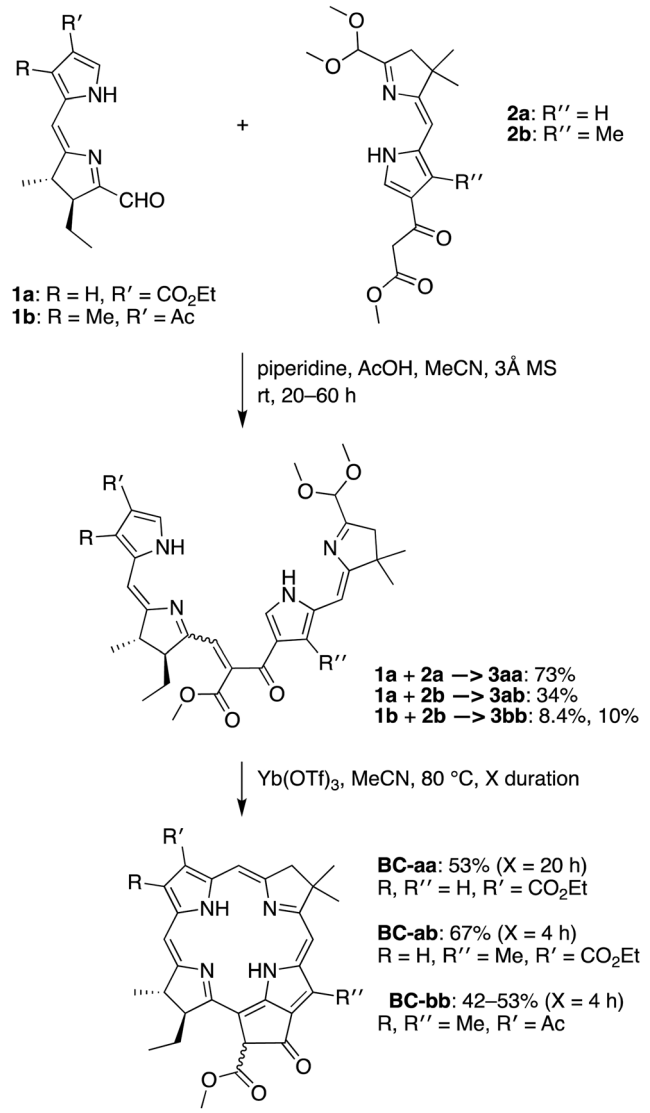
Macrocycle formation – comparison of rates

The reaction of enone **3ab** in the double-ring closure step (Scheme 5) was investigated under the same conditions recently optimized for **3aa-*E***. The conditions are enone (0.2 mM) and $Yb(OTf)_3$ (2.0 mM) in acetonitrile at 80 °C for 4 h.[6] (The preparative conversion of **3aa-*E*** to **BC-aa** was originally carried out for 20 h,[4] although 4 h is now known to suffice.[6]) Samples were removed periodically from the reaction mixture, diluted, and examined by absorption spectroscopy. The yield of bacteriochlorophyll analogue **BC-ab** was assessed by the strong and characteristic long-wavelength (Q_y) absorption band at ~760 nm (assuming ε = 72 100 M^{-1} cm^{-1} on the basis of data for **BC-aa**). The reaction proceeded smoothly. The yield leveled off at 72% within 3–4 h, with $t_{1/2}$ = 37 min (Fig. 2). The results were quite similar to those for conversion of **3aa-*E*** to **BC-aa** (77% maximum yield, $t_{1/2}$ = 43 min).[6] Upon implementation at 50 °C, the double-ring closure of **3ab** gave **BC-ab** in 67% yield although the reaction time was extended to 48 h (Fig. 2). The $t_{1/2}$ value at 50 °C was 300 min, approximately 8 times slower than that performed at 80 °C.

The 8-fold slower rate with a 30 °C decrease in temperature comports with the heuristic that a 10 °C change (increase, decrease) in temperature gives a 2-fold change (increase, decrease) in reaction rate. Surprising here, however, is that **3aa** and **3ab** gave identical rates. In other words, the presence of the methyl group on the β-position of the pyrrole in **3ab** gave no observable effect on the double-ring closure *versus* that of **3aa** where no methyl group was present. To the extent that the Nazarov cyclization would be affected by a more electron-rich (*i.e.*, methyl-substituted) pyrrole more so than the other reactions (S_EAr, elimination of methanol) of the double-ring closure, then the Nazarov cyclization appears to not be the rate-determining step of the overall process. A less likely interpretation is that the methyl group causes opposite, cancelatory effects in distinct steps with no net manifestation. It warrants emphasis that the kinetic studies performed here assess formation of the bacteriochlorin chromophore, the end-product of the overall process, and not the Nazarov cyclization itself. Additional studies with simpler systems will be required to probe these issues.

Nazarov cyclization studies

Further perspectives concerning the data shown in Fig. 2 are provided by literature results of other systems. Frontier and coworkers carried out studies of the cyclization of members of a family of 1,4-dien-3-ones (**I** → **V**, Scheme 6).[32] The reaction rate was profoundly accelerated with increased electron-releasing effect of substituent R^5; the time to completion ranged from ≪1 h to 240 h across the series: 2,4,6-trimethoxyphenyl (fastest) < 4-methoxyphenyl < 2-furyl < 3-methoxyphenyl < phenyl < cyclohexyl (slowest). The effect was generally opposite for $R^{1,2}$ substituents, with slower rates observed with more electron-rich substituents. The corresponding groups in the enones **3aa**, **3ab** and **3bb** are shown upon complexation with $Yb(OTf)_3$ as well as following Nazarov cyclization and loss of the coordinated metal ion. Both the corresponding R^5 and $R^{1,2}$ groups are dihydrodipyrrins (*i.e.*, **VI** corresponds to **II**, **VII** corresponds to **V**);



Scheme 5 Knoevenagel condensation and double-ring closure.

however, the R^5 equivalent group (AD half) is attached *via* the pyrrolinyl group whereas the $R^{1,2}$ equivalent groups (CB half) constitute the pyrrole moiety of the dihydrodipyrrin. In other words, the AD dihydrodipyrrin and the CB dihydrodipyrrin comprise two groups in the dienone unit of **3** but are situated in reverse manner with each other. The pyrrole and pyrroline groups are electron-rich and electron-deficient, respectively, yet also are in resonance in a dihydrodipyrrin *via* the intervening double bond that joins the two motifs (as revealed by studies of a set of hydrodipyrrins[33]); hence, the electronic interactions of the AD and CB halves in influencing the course of the Nazarov cyclization are unclear. Further studies of similar substrates that cannot undergo macrocyclization are required to better understand these issues.

Macrocycle preparation

To prepare bacteriochlorophyll analogue **BC-ab** at an isolable scale, the reaction of enone **3ab** was carried out under the same

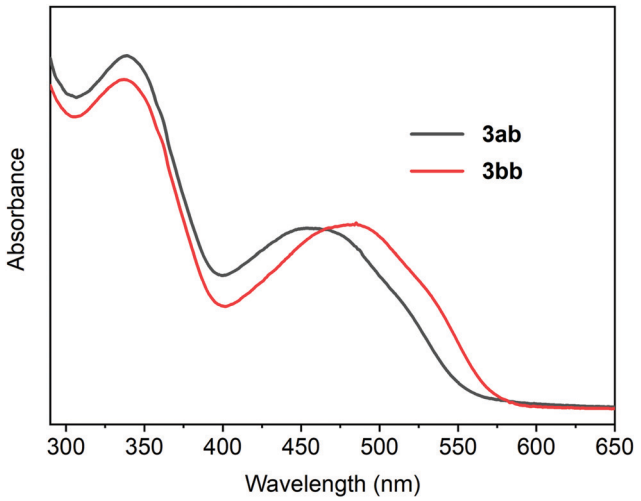


Fig. 1 Absorption spectra in toluene at room temperature of enones **3ab** and **3bb**.

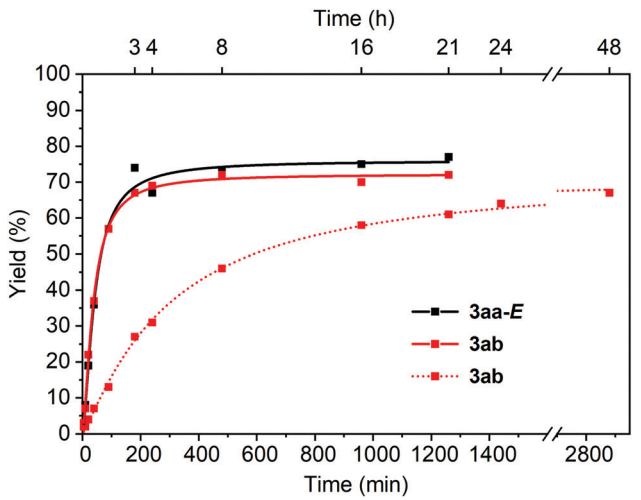
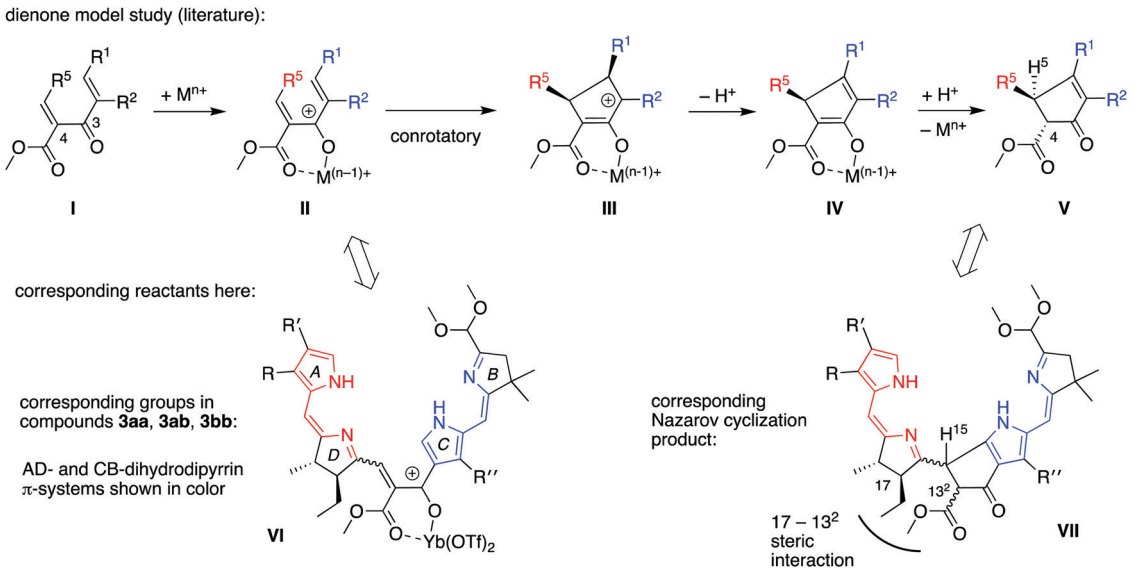


Fig. 2 Yield of bacteriochlorophyll analogues over time from enones **3aa-*E*** and **3ab** in the double-ring closure reaction. The reactions were conducted at 0.2 mM enone and 2 mM $Yb(OTf)_3$ in acetonitrile at 80 °C (solid line) or 50 °C (dotted line). The data for **3aa-*E*** were published previously.[6]

conditions as for the timecourse study, and stopped at 4 h (Scheme 5). Purification by chromatography afforded **BC-ab** in 67% yield along with a trace amount (*ca.* 1.2%) of the by-product **BC-ab-pyro** wherein the 13^2-carbomethoxy group was lost (Chart 2). The loss of the carbomethoxy group, which occurred here to only slight extent, is a well-known reaction. The reaction is generally carried out at elevated temperature (such as in hot pyridine[34] or collidine[35]), hence the traditional use of the "pyro" label for the resulting 13^2-des(carbomethoxy) derivatives of (bacterio)chlorophylls. The reaction is known more so for chlorophylls than for bacteriochlorophylls, a distinction that may stem from the greater focus over the years on the former *versus* the latter as well as the appearance of pyropheophorbides (derived from chlorophylls) in certain



Scheme 6 Nazarov cyclization reaction course (**I–V**)[32] and corresponding structures here (**VI**, **VII**).

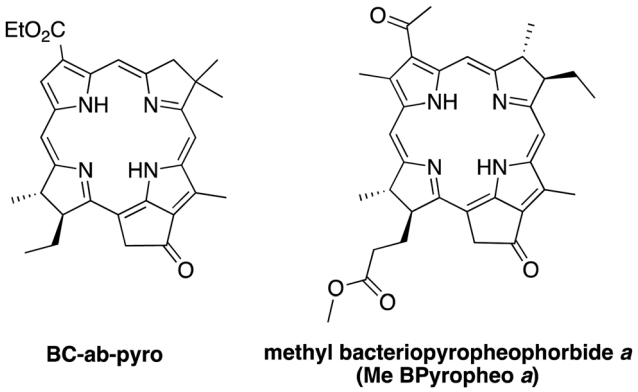


Chart 2 Macrocycles lacking the 13^2-carbomethoxy group.

photosynthetic organisms.[36,37] (The terminology is that "pheo" refers to the free base macrocycle, "pyro" indicates loss of the 13^2-carbomethoxy group, and "phorbide" refers to alteration of the 17^3 ester substituent – *i.e.*, replacement of the phytyl group.) Bacteriochlorophylls *c–f*, which are true chlorins rather than bacteriochlorins, lack the 13^2-carbomethoxy group (which is removed during biosynthesis[38]), and are found abundantly in the chlorosomes of green bacteria.[1] Regardless, methyl bacteriopyropheophorbide *a* is a known compound (Chart 2).[39] Despite insufficient quantity preventing full characterization, the identity of **BC-ab-pyro** could still be verified on the basis of (1) the appearance of two diastereotopic 13^2 methylene doublets at 5.01 and 5.02 ppm in the ^{1}H NMR spectrum; (2) a peak at m/z = 511.2692 $(M + H)^+$ upon accurate mass analysis; and (3) diminution of the peak at 1740 cm^{-1} representing the methyl ester (a value of 1741 cm^{-1} is assigned for the methyl ester group in pheophorbide *a*[40]) and comparison of the IR spectrum to that of **BC-ab** (Fig. 3).

The double-ring closure of enone **3bb** was examined under the same conditions (0.2 mM **3bb** and 2 mM $Yb(OTf)_3$ in acetonitrile at 80 °C for 4 h), whereupon the desired bacteriochlorophyll analogue **BC-bb** was obtained in 42% yield (Scheme 5).

One objective for synthetic routes to the native photosynthetic pigments is to achieve streamlined transformations. In this regard, enone **3bb** was prepared in a second batch under the same conditions for the Knoevenagel condensation of **1b** and **2b**. The isolated product was composed of enone **3bb** along with compound **2b** and the aforementioned unknown species; ^{1}H NMR analysis with use of mesitylene as an internal standard indicated that the purity of **3bb** was 20%, which corresponds to a yield from **2b** of 8.4%. The crude sample of **3bb** (20% purity)

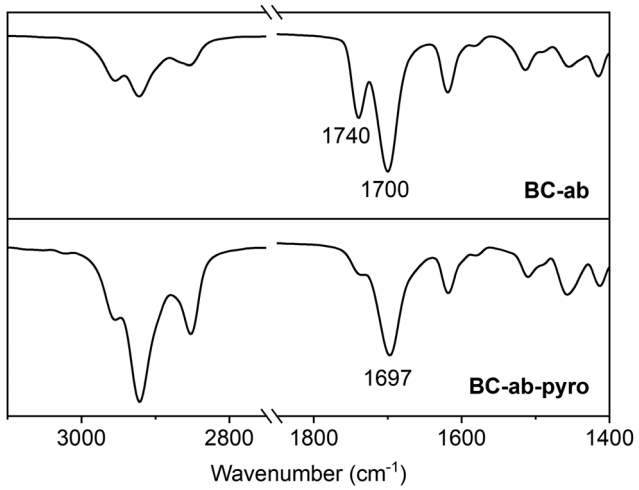


Fig. 3 IR spectra of **BC-ab** (top) showing a band corresponding to the 13^2-methoxycarbonyl group at 1740 cm^{-1} (the value is 1741 cm^{-1} in pheophorbide *a*[40]) and **BC-ab-pyro** (bottom) formed from *in situ* decarbomethoxylation of **BC-ab**. Bands at 1700 cm^{-1} and 1697 cm^{-1} can be assigned to the 13-ketone (1702 cm^{-1} and 1685 cm^{-1} in pheophorbide *a* and pyropheophorbide *a*, respectively[40]).

was subjected to double-ring closure, whereupon bacteriochlorin **BC-bb** was obtained in 53% yield (on the basis of the quantity of **3bb** in the crude sample), which is comparable to that reported above for **BC-ab** and previously for **BC-aa**. While the presence of an unknown impurity and unreacted starting material was undesirable, the ability to use a very crude sample for the double-ring closure indicates the robustness of the process. In neither reaction of pure **3bb** nor crude **3bb** was any des(carbomethoxy) byproduct observed, although the scale of each reaction was ~10-fold smaller than for the case of the synthesis of **BC-ab**.

Characterization – structural features

Five synthetic intermediates (**7**, **8**, **10**, **11**, **15**) were characterized by single-crystal X-ray crystallography (Fig. 4). Compounds **7** and **8** show substitution of the bromine at the 4-position of the pyrrole. Compound **10** shows the elaboration of the nitro-hexanone motif for formation of the pyrroline ring. Compound **11** shows the installation of the β-ketoester at the pyrrole 4-position. Compound **15** shows regioselective introduction of the iodine atom at the pyrrole 2-position.

The bacteriochlorophyll analogue **BC-ab** was analyzed by ^{1}H NMR spectroscopy and NOESY. The sample was comprised (as expected[6]) of two 13^2-epimers, of which the dominant epimer (91%) possesses a *trans–trans* configuration with respect to the three methine protons in moving from position 18 to 17 to 13^2 (*i.e.*, spanning ring D to ring E). As depicted in Fig. 5, the *trans–trans* configuration in the dominant epimer was verified by correlations of the proton at position 13^2 with those (denoted as 17^1 and 17^2) in the ethyl substituent located on the same face of the macrocycle. A correlation between the proton at position 13^2 with that at position 17 on the opposite face of the macrocycle is also observed due to their close proximity. Meanwhile, for the minor epimer, the proton at position $13^{2\text{-epi}}$ only exhibits a correlation with that at position 17 but not with those in the ethyl group at position 17, supporting the *trans–cis* stereochemistry of the 18-17-13^2 cluster. The minor epimer (9%) thus has a *trans–cis* configuration across the same positions. For **BC-bb**, an initial study by ^{1}H NMR spectroscopy suggested an epimeric ratio of 89 : 11, which is closely similar to that of **BC-ab**. Further stereochemical examination of compound **BC-bb** by NOESY was not conducted due to insufficient sample.

The *trans* stereochemistry of the substituents in a pyrroline ring can be probed by analysis of the first-order multiplets of the two methine protons. It is well known that the coupling

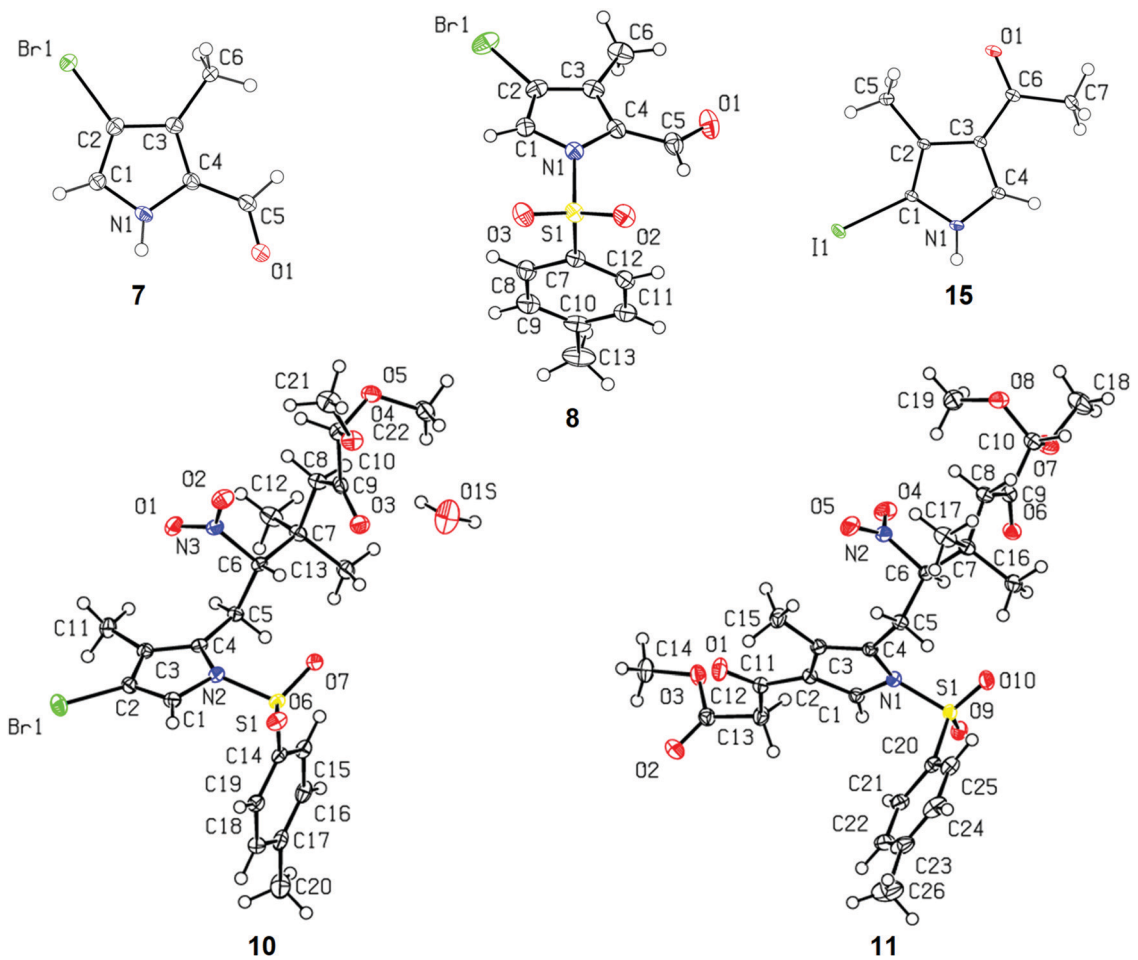


Fig. 4 ORTEP diagrams of five intermediates with thermal ellipsoids drawn at the 50% probability level.

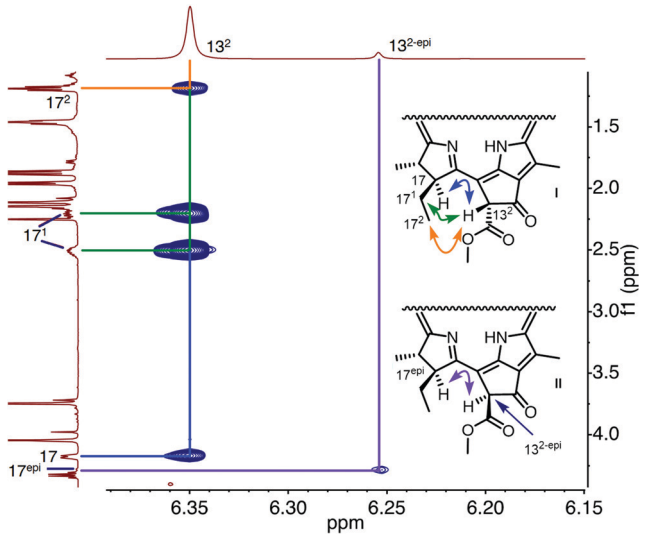
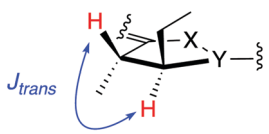


Fig. 5 Enlarged region of the NOESY spectrum of **BC-ab** sample showing the correlations supporting the configuration assignment of the two epimers.

constant (J) of two vicinal protons with *trans* stereochemistry in a five-membered rigid ring varies from 2.5 to 4.6 Hz, whereas the value for *cis* stereochemistry is 7.4–9.2 Hz (values for a bicyclo[2.2.1]heptene).[41] These values are found to be 1.8, 2.0, and 1.6 Hz for chlorophyll *a* (in acetone-d_6 or THF-d_8), pheophytin *a* (in $CDCl_3$), and methyl pheophorbide *a* (in $CDCl_3$), respectively.[42] The values recorded for a lactone–pyrrole, a dihydrodipyrrin, three enones, and three bacteriochlorophyll analogues are listed in Table 1. The values were largest for the precursors **17** and **19** (4.1 and 3.8 Hz, respectively), intermediate for the enones **3** (~3.7 Hz), and lowest for the bacteriochlorophyll analogues (~3.0 Hz). In all cases, the J values were in the range expected for *trans* stereochemistry.

While the characterization of the epimers is clear, it is not clear when the epimers arise during the course of the double-ring closure, whether the formation is kinetically or thermodynamically controlled, and/or whether the observed ratio derives from epimerization of the intact macrocycles on routine handling following completion of the synthesis. The two stereocenters (positions 4 and 5) derived from model 1,4-dien-3-ones are set at distinct times in the reaction course (Scheme 6); at position 5 during the conrotatory electrocyclization of the pentadienyl cation, and at position 4 upon protonation and loss of the coordinating metal ion.[43] In the Nazarov cyclization product derived from enones **3**, the subsequent loss of H^{15} upon aromatization abolishes one stereocenter (corresponding to loss of stereochemistry in model dienone at position 5). The stereocenter at position 13^2 is expected to form upon protonation and displacement of the coordinated ytterbium ion. Steric interactions of the ethyl group at position 17 must favor the observed *trans* (13^2-17) stereochemistry. Epimerization of members of the chlorophyll family is well studied but relatively little is known concerning bacteriochlorophylls and derivatives, although data suggest the rate for the intact macrocycles is quite slow.[44–48] Separate studies are required to explore possible epimerization at the 13^2-position of the intact synthetic bacteriochlorophyll analogues.

Table 1 Coupling constants for methine protons in pyrroline rings



Compound	Structure	J (Hz)
17	Lactone–pyrrole	4.1
18	Ene–lactone–pyrrole	—[a]
19	Dihydrodipyrrin	3.8
1b	Dihydrodipyrrin	—[b]
3aa	Enone	3.7
3ab	Enone	3.7
3bb	Enone	3.6
BC-aa	Bacteriochlorophyll analogue	3.1
BC-ab	Bacteriochlorophyll analogue	3.0
BC-bb	Bacteriochlorophyll analogue	3.0

[a] Not determined because of the broadening of signals of interest. [b] Not determined because of second-order effects of signals of interest.

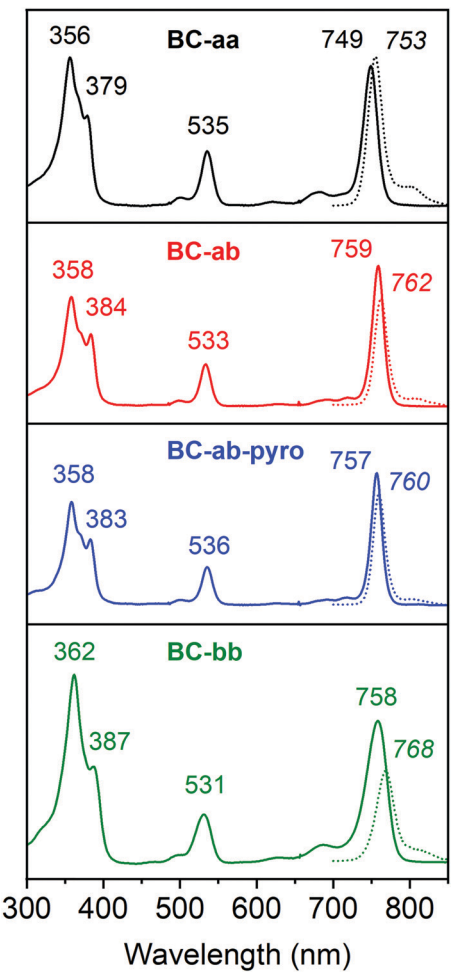


Fig. 6 Absorption spectra (solid lines) and fluorescence spectra (dotted lines) in toluene at room temperature. The spectra of **BC-aa** were reported previously.[4]

Table 2 Spectral properties of bacteriochlorophylls and analogues[a]

Compound	λ_{abs}(B), nm	$\lambda_{abs}(Q_y)$, nm	Q_y (abs) fwhm, nm	I_{Q_y}/I_B	λ_{em}	Stokes shift, nm	Φ_f
BC-ab	358, 384	759	19	1.28	762	3	0.16
BC-ab-pyro	358, 383	757	18	1.27	760	3	0.17
BC-bb	362, 387	758	27	0.75	768	10	0.13
Bacteriopheophytin *a*[b]	362, 389	758	31	0.69	768	10	0.10
Me BPyropheo *a*[c]	360	754	36	0.62	761	7	—
Me BPyropheo *a*[d]	361	754	28.5	0.61	767	13	0.16

[a] All data are from samples in toluene at room temperature. [b] Data in CH_2Cl_2.[39] [c] Data in toluene.[49] [d] Data in CH_2Cl_2.[51]

Characterization – electronic features

The absorption and fluorescence features of **BC-ab**, **BC-ab-pyro**, and **BC-bb** in toluene are shown in Fig. 6. The bacteriochlorophyll analogues **BC-ab** and **BC-ab-pyro** exhibit (expected) similar features to each other in terms of the position of the near-ultraviolet (B) and long-wavelength (Q_y) bands (358, 384 and 759 nm in **BC-ab** *versus* 358, 383 and 757 nm in **BC-ab-pyro**), full-width-at half-maximum (fwhm) of the Q_y band (19 *versus* 18 nm), intensity ratio of the Q_y and B bands (I_{Q_y}/I_B = 1.28 *versus* 1.27), and Stokes shift (3 nm in both cases). The long-wavelength Q_y absorption peak of **BC-ab** (or **BC-ab-pyro**) is bathochromically shifted by ~10 nm relative to that of **BC-aa**, indicating the mild auxochromic effect of the 12-methyl group. Compound **BC-bb**, which bears 3-acetyl and 2,12-dimethyl groups, exhibits no significant further bathochromic shift of the Q_y band (758 nm) *versus* that with 3-carboethoxy and 12-methyl groups (**BC-ab**), although the band is considerably broadened with fwhm = 27 nm. The broadening of the Q_y band is accompanied by a diminished peak intensity, which is reflected in the lower I_{Q_y}/I_B ratio (0.75). The Stokes shift of 10 nm for **BC-bb** is an inevitable consequence of the broader Q_y band. Still, all the photophysical data listed for **BC-bb** closely resemble those of bacteriopheophytin *a*.[49,50] The fluorescence quantum yield (Φ_f) of **BC-ab** or **BC-ab-pyro** was found to be 0.16 or 0.17, respectively, whereas that of **BC-bb** is only 0.13, which is close to the literature value[49] for bacteriopheophytin *a* (0.10). The spectral features for the bacteriochlorophyll analogues (Charts 1 and 2) are listed in Table 2.[39,49,51]

Conclusions

Synthesis of native photosynthetic bacteriochlorophylls requires a strategy to construct the macrocycle skeleton, install the *trans*-dialkyl groups in the (B, D) pyrroline rings, and introduce the various substituents in the (A, C) pyrrole rings. The present work demonstrates access to the 12-methyl group but reveals limitations in the installation of the 2-methyl-3-acetyl groups. The introduction of the 12-methyl group gave a lower yield in the Knoevenagel reaction but had no effect on the double-ring cyclization process. The introduction of the 2-methyl-3-acetyl groups gave surprisingly poor yields in the Petasis methenylation and Riley oxidation as well as the Knoevenagel condensation, whereas the double-ring cyclization proceeded in yield comparable to that of unsubstituted substrates. The diminished yields in the Knoevenagel process but not in the double-ring cyclization process is surprising. The strategy for creating the core bacteriochlorophyll skeleton, where *trans*-dialkyl groups in the pyrroline rings (demonstrated for ring D) are installed at an early stage of the synthetic plan, appears to be quite robust and versatile. Future work will focus on improving yields of intermediates and also incorporating the full complement of substituents characteristic of the native photosynthetic pigments.

Experimental section

General methods

All chemicals from commercial suppliers were used as received without further purification. Silica used for column chromatography was 230–400 mesh (60 Å). THF for use as a reaction medium was freshly distilled from sodium/benzophenone ketyl. Anhydrous acetonitrile used in coupling reactions was degassed during the early time of the reaction course, whereas that for double-ring closure was degassed in advance before being stored in a glovebox. Other solvents (reagent grade) were used as received from commercial suppliers. The temperature (*e.g.*, 80 °C) reported for each double-ring closure process (timecourse or synthetic preparation) was recorded internal to the reaction vessel (*i.e.*, of the reaction mixture itself) as opposed to that of the external heating source. Compounds **5**,[9] **6**,[14] **7**,[13–15] **8**,[15] and **10**[15] are known and were prepared here *via* alternative or revised procedures. Compounds **1a**,[4] **9**,[17] **14**,[9] and **16**[4] were prepared as described in the literature. Accurate mass analysis was achieved by high-resolution mass spectrometry using the electrospray ionization time-of-flight method (HRMS-ESI-TOF). The temperatures (*e.g.*, 80 reported for the double-ring closure processes (timecourse study and synthetic preparation).

Synthesis of the BC half

3-Methyl-1-(triisopropylsilyl)pyrrole (5). Following a reported procedure,[9] a solution of **4** (11.15 g, 50.0 mmol) in distilled THF (115 mL) at −78 °C under argon was treated portionwise with NBS (8.90 g, 50 mmol) over a few minutes. The reaction mixture was stirred at −78 °C until TLC analysis (silica, hexanes) indicated the absence of starting material. The reaction mixture was then treated with saturated aqueous $NaHCO_3$ (120 mL) and extracted with diethyl ether (80 mL × 3). The combined organic extract was dried (Na_2SO_4) and concentrated to give 3-bromo-1-(triisopropylsilyl)pyrrole as a light-yellow oil. The crude oil was dissolved in anhydrous THF (185 mL), cooled to −78 °C under argon, and treated dropwise with *n*-BuLi (38.0 mL, 1.6 M in

hexanes, 61 mmol). The reaction mixture was stirred for 30 min at −78 °C under argon. Then, MeI (9.20 mL, 147 mmol) was added dropwise into the reaction mixture. The resulting mixture was stirred for 20 min at −78 °C under argon and then allowed to warm to room temperature. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (150 mL), extracted with ethyl acetate (80 mL × 3), dried (Na_2SO_4), and concentrated to a yellow oil. The oil was chromatographed [silica, hexanes] to afford a colorless oil (6.84 g, 58%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.10 (d, J = 7.5 Hz, 18H), 1.38–1.47 (m, 3H), 2.13 (s, 3H), 6.14 (s, 1H), 6.53 (s, 1H), 6.69 (t, J = 2.5 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 11.8, 18.0, 110.2, 112.0, 120.7, 121.9, 124.2; HRMS-ESI-TOF m/z: $[M + H]^+$ calcd for $C_{14}H_{28}NSi$ 238.1986; found 238.1981.

3-Methyl-1*H*-pyrrole-2-carbaldehyde (6). Following a reported procedure,[9] a mixture of **5** (6.84 g, 28.8 mmol) and TBAF (58 mL, 1 M in THF) was stirred at 0 °C under argon. The starting material was consumed after 10 min as determined by TLC analysis. The reaction mixture was extracted with diethyl ether, washed with water and brine, then dried (Na_2SO_4) and concentrated to a light-yellow oil. The crude product was dissolved in anhydrous 1,2-dichloroethane (7 mL) and then cooled to 0 °C under argon. In a second flask, the Vilsmeier–Haack reagent was prepared[10] by dropwise addition of $POCl_3$ (6.5 mL, 70 mmol) into anhydrous DMF (5.5 mL) at 0 °C under argon. The resulting slurry was stirred, allowed to warm to room temperature for 15 min, and then diluted with anhydrous 1,2-dichloroethane (15 mL). The solution in the first flask was transferred to the flask containing the Vilsmeier–Haack reagent at 0 °C under argon. The reaction mixture was stirred at reflux in a heating mantle for 15 min and then allowed to cool to room temperature. The resulting mixture was hydrolyzed by treatment with saturated aqueous NaOAc (45 mL) for 20 min under argon in an oil bath at 100 °C. After allowing to cool to room temperature, the mixture was extracted with CH_2Cl_2 (80 mL × 3). The organic extract was dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (1 : 1), TLC R_f = 0.51] to afford a pale-yellow solid (1.54 g, 49%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.39 (s, 3H), 6.13 (s, 1H), 7.01 (s, 1H), 9.45 (br s, 1H), 9.63 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 10.7, 112.9, 125.9, 129.7, 132.8, 177.7; HRMS-ESI-TOF m/z: $[M + H]^+$ calcd for C_6H_8NO 110.0600; found 110.0600.

4-Bromo-3-methyl-1-tosyl-1*H*-pyrrole-2-carbaldehyde (8). Following a reported procedure[13] with modifications, a solution of **6** (1.54 g, 14.1 mmol) in anhydrous DMF (88 mL) was treated portionwise with DBDMH (2.10 g, 7.34 mmol) at 0 °C under argon, then allowed to warm to room temperature. After 5 h, the mixture was quenched by the addition of 5% aqueous $KHSO_4$ solution and then extracted with ethyl acetate (70 mL × 3). The combined organic extract was washed with water and brine, dried (Na_2SO_4), and concentrated under high vacuum to afford **7** as a yellow solid. Characterization by ^{1}H NMR spectroscopy indicated adequate purity for use in the next step. The crude **7** was dissolved in CH_2Cl_2 (82 mL) at 0 °C under argon and tosylated[16] by treatment with triethylamine (3.7 mL, 26.5 mmol), 4-dimethylaminopyridine (0.20 g, 1.64 mmol), and *p*-toluenesulfonyl chloride (3.20 g, 16.8 mmol). After being stirred for 24 h at room temperature, the reaction mixture was quenched with water (100 mL) and extracted with CH_2Cl_2 (50 mL × 3). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography [silica, hexanes/ethyl acetate (5 : 1), TLC R_f = 0.53] to give pale-white crystals (2.79 g, 58% from **6**). M.p. 151–153 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.30 (s, 3H), 2.43 (s, 3H), 7.34 (d, J = 8.5 Hz, 2H), 7.55 (s, 1H), 7.76 (d, J = 8.5 Hz, 2H), 10.14 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 12.0, 21.9, 106.2, 126.7, 127.5, 129.0, 130.5, 135.1, 136.3, 146.4, 180.1; HRMS-ESI-TOF m/z: $[M + H]^+$ calcd for $C_{13}H_{13}BrNO_3S$ 341.9794; found 341.9794.

6-(4-Bromo-3-methyl-1-tosyl-1*H*-pyrrol-2-yl)-1,1-dimethoxy-4,4-dimethyl-5-nitrohexan-2-one (10). Following a reported procedure[15] with modifications, a ground mixture of **8** (1.30 g, 3.80 mmol), KOAc (0.29 g, 3.0 mmol), and $MeNH_2$·HCl (0.20 g, 3.0 mmol) was suspended in absolute ethanol (1.7 mL) and acetic acid (134 μL), and then treated with CH_3NO_2 (1.00 mL, 18.7 mmol). The mixture was stirred at room temperature under argon for 24 h. The resulting mixture was washed with water (70 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic extract was concentrated under reduced pressure. The crude material, which was found to consist of unreacted starting material, was treated again with KOAc (0.29 g, 3.0 mmol), $MeNH_2$·HCl (0.20 g, 3.0 mmol), absolute ethanol (1.7 mL), acetic acid (134 μL), and CH_3NO_2 (1.00 mL, 18.7 mmol) at room temperature for 24 h, whereupon all of the starting material disappeared as confirmed by ^{1}H NMR analysis (starting material: –CHO: s, δ 10.14 ppm; product CH = $CHNO_2$: d, J = 13.5 Hz, δ 8.56 ppm). Then, water (70 mL) was added to the reaction mixture. The combined mixture was extracted with ethyl acetate (50 mL × 4). The organic extract was washed with brine, dried (Na_2SO_4), concentrated and dried overnight under high vacuum to obtain an orange-yellow solid. The crude solid was dissolved in $CHCl_3$/i-PrOH (3 : 1, 25.4 mL), then the solution was cooled to 0 °C under argon and treated with silica (4.5 g) and $NaBH_4$ (287 mg, 7.6 mmol). After stirring for 20 min, the reaction mixture was quenched by the addition of cold saturated aqueous NH_4Cl (20 mL). The mixture was extracted with ethyl acetate (50 mL × 3). The organic extract was washed with brine, dried (Na_2SO_4), concentrated and dried overnight under high vacuum to obtain a pale-yellow solid. A mixture of the resulting solid and **9** (1.16 g, 7.3 mmol) was treated with DBU (11.5 mL, 77 mmol) at room temperature under argon for 1 h. The reaction mixture was quenched by the addition of cold saturated aqueous NH_4Cl (20 mL) and extracted with ethyl acetate (50 mL × 3). The organic extract was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography [silica, hexanes/ethyl acetate (5 : 1), TLC R_f = 0.26] to give a pale-yellow solid (1.150 g, 55%). M.p. 115–117 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (s, 3H), 1.28 (s, 3H), 1.87 (s, 3H), 2.42 (s, 3H), 2.65 (d, J = 18.5 Hz, 1H), 2.74 (d, J = 18.5 Hz, 1H), 3.18 (dd, J = 15.5, 2.5 Hz, 1H), 3.34 (dd, J = 15.5, 12 Hz, 1H), 3.43 (s, 3H), 3.44 (s, 3H), 4.35 (s, 1H), 5.17

(dd, J = 12, 2.5 Hz, 1H), 7.27 (s, 1H), 7.32 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.5 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 10.6, 21.8, 23.7, 23.9, 25.8, 36.7, 44.2, 55.20, 55.22, 94.3, 104.8, 105.8, 122.5, 125.0, 125.9, 126.6, 130.5, 135.8, 145.6, 203.1; HRMS-ESI-TOF m/z: $[M + H]^+$ calcd for $C_{22}H_{30}BrN_2O_7S$ 545.0952; found 545.0945.

Methyl 3-(5-(6,6-dimethoxy-3,3-dimethyl-2-nitro-5-oxohexyl)-4-methyl-1-tosyl-1*H*-pyrrol-3-yl)-3-oxopropanoate (11). Following a reported procedure[3] with slight modification, a mixture of **10** (1.09 g, 2.0 mmol), methyl potassium malonate (0.47 g, 3.0 mmol), Xantphos (0.58 g, 1.0 mmol), $MgCl_2$ (0.29 g, 3.0 mmol), and imidazole (0.26 g, 3.8 mmol) was placed in a 25 mL Schlenk flask under argon. Distilled THF (20 mL) was added followed by triethylamine (420 μL). After being degassed by three freeze–pump–thaw cycles, $Pd(OAc)_2$ (0.22 g, 1.0 mmol) and $Co_2(CO)_8$ (0.17 g, 0.5 mmol) were added. The flask was sealed immediately and heated under argon in an oil bath at 70 °C. After 24 h, the reaction mixture was diluted with ethyl acetate and then filtered through a Celite pad. The filtrate was washed with water and brine, dried (Na_2SO_4), concentrated and chromatographed [silica, hexanes/ethyl acetate (1 : 1), TLC R_f = 0.51] to afford a yellow solid (870 mg, 77%). M.p. 124–126 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.21 (s, 3H), 1.27 (s, 3H), 2.08 (s, 3H), 2.43 (s, 3H), 2.64 (d, J = 18.5 Hz, 1H), 2.73 (d, J = 18.5 Hz, 1H), 3.00 (dd, J = 15.5, 2.5 Hz, 1H), 3.35 (dd, J = 15.5, 12 Hz, 1H), 3.41 (s, 3H), 3.42 (s, 3H), 3.70–3.82 (m, 5H), 4.36 (s, 1H), 5.19 (dd, J = 12, 2.5 Hz, 1H), 7.34 (d, J = 8 Hz, 2H), 7.60 (d, J = 8 Hz, 2H), 7.89 (s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 10.9, 21.8, 23.7, 23.9, 24.5, 36.7, 44.1, 47.4, 52.6, 55.17, 55.20, 93.8, 104.8, 125.6, 126.2, 126.69, 126.73, 130.1, 130.7, 135.2, 146.2, 167.8, 187.6, 203.1; HRMS-ESI-TOF m/z: $[M + H]^+$ calcd for $C_{26}H_{35}BrN_2O_{10}S$ 567.2007; found 567.2005.

Methyl 3-(5-(6,6-dimethoxy-3,3-dimethyl-2-nitro-5-oxohexyl)-4-methyl-1*H*-pyrrol-3-yl)-3-oxopropanoate (12). Following a reported procedure,[15] a mixture of **11** (354 mg, 0.625 mmol) and TBAF (1 mL, 1 M in THF) was heated in an oil bath at 65 °C for 1.5 h, then quenched by the addition of saturated aqueous $NaHCO_3$ (2 mL) and extracted with ethyl acetate (1 mL × 3). The organic extract was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography [silica, hexanes/ethyl acetate (1 : 1), TLC R_f = 0.26] to give a pale-yellow oil (208 mg, 81%). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.14 (s, 3H), 1.23 (s, 3H), 2.22 (s, 3H), 2.61 (d, J = 18.5 Hz, 1H), 2.74 (d, J = 18.5 Hz, 1H), 2.98 (dd, J = 15.5, 2.5 Hz, 1H), 3.26 (dd, J = 15, 11.5 Hz, 1H), 3.42 (s, 3H), 3.43 (s, 3H), 3.726 (s, 3H), 3.731(s, 2H), 4.35 (s, 1H), 5.11 (dd, J = 11.5, 2.5 Hz, 1H), 7.27 (d, J = 3.4 Hz, 1H), 8.57 (br s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 10.4, 24.1, 24.3, 36.5, 45.0, 46.9, 52.3, 55.2, 93.9, 104.6, 118.5, 123.3, 125.1, 125.7, 168.9, 187.8, 203.8; HRMS-ESI-TOF m/z: $[M + H]^+$ calcd for $C_{19}H_{29}N_2O_8$ 413.1918; found 413.1912.

1-(1,1-Dimethoxymethyl)-8-(3-methoxy-1,3-dioxopropyl)-3,3,7-trimethyl-2,3-dihydrodipyrrin (2b). Following a reported procedure,[15] a solution of **12** (208 mg, 0.504 mmol) in distilled THF (5 mL) was treated with freshly prepared $NaOCH_3$ (109 mg, 2 mmol) in a 25 mL flask and bubbled with argon for 15 min. In a 50 mL flask, NH_4OAc (3.95 g, 51 mmol) in distilled THF (12.8 mL) was bubbled with argon for 15 min before a solution of $TiCl_3$ (20 wt% in 2N HCl, 3.0 mL, 2.4 mmol) was added. The mixture was stirred for 30 min. Then, the solution in the first flask was transferred *via* cannula to the buffered $TiCl_3$ mixture in the second flask. The reaction mixture at room temperature was stirred continuously under argon for 24 h. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution, and filtered through a Celite pad. The filter cake was washed with ethyl acetate (3 mL × 3). The filtrate was washed with water and brine, dried (Na_2SO_4), concentrated and chromatographed [silica, CH_2Cl_2/ethyl acetate (1 : 1), TLC R_f = 0.73] to afford a yellow, oily solid (49.9 mg, 27%). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.23 (s, 6H), 2.36 (s, 3H), 2.63 (s, 2H), 3.44 (s, 6H), 3.73 (s, 3H), 3.77 (s, 2H), 5.02 (s, 1H), 5.86 (s, 1H), 7.44 (d, J = 3.5 Hz, 1H), 11.12 (br, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 10.8, 29.3, 40.5, 47.5, 48.6, 52.5, 54.6, 102.5, 104.1, 119.5, 123.3, 126.3, 129.9, 161.1, 168.9, 175.5, 187.6; HRMS-ESI-TOF m/z: $[M + H]^+$ calcd for $C_{19}H_{27}N_2O_5$ 363.1915; found 363.1913.

Synthesis of the AD half

4-Acetyl-2-iodo-3-methylpyrrole (15). Following a general procedure[9] with modification, a solution of **14** (7.35 g, 60 mmol) in DMF (132 mL) at 0 °C was treated with NIS (13.50 g, 60 mmol) in portions over 15 min. The reaction mixture was vigorously stirred at 0 °C for 1 h, followed by dilution with water (100 mL). The resulting solution was extracted with Et_2O (150 mL × 4). The organic extract was dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (1 : 2), 6.5 cm × 40 cm] to afford a slightly yellow solid (8.33 g, 56%). M.p. (dec.) 95–100 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.27 (s, 3H), 2.39 (s, 3H), 7.45 (d, J = 3.2 Hz, 1H), 8.18 (s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 14.0, 27.4, 70.2, 125.2, 126.4, 128.2, 193.2; HRMS-ESI-TOF m/z: $[M + H]^+$ calcd for C_7H_9INO, 249.9723; found 249.9719.

(3*S*,4*S*)-5-((4-Acetyl-3-methyl-1*H*-pyrrol-2-yl)methylene)-3-ethyl-4-methyldihydrofuran-2(3*H*)-one (17). Following a general procedure[4] with modifications, a 500 mL Schlenk flask was charged with samples of **15** (4.50 g, 18.0 mmol), **16** (2.52 g, 18.0 mmol), $BnNEt_3Cl$ (5.00 g, 22.0 mmol), and Et_3N (21 mL) in acetonitrile (102 mL). Three cycles of freeze–pump–thaw were applied to the mixture followed by the addition of $Pd(PPh_3)_4$ (1.04 g, 0.900 mmol). The resulting mixture was subjected to one more freeze–pump–thaw cycle and then stirred in an oil bath at 80 °C for 18 h. The mixture was allowed to cool to room temperature, diluted by the addition of water (123 mL), and extracted with CH_2Cl_2 (4 × 82 mL). The combined organic extract was dried (Na_2SO_4), concentrated and chromatographed [silica, hexanes/ethyl acetate (1 : 1), 6.5 cm × 40 cm, TLC R_f = 0.24] to deliver a brown paste (1.78 g, 38%). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.06 (t, J = 7.5 Hz, 3H), 1.12 (d, J = 7.0 Hz, 3H), 1.66–1.76 (m, 1H), 1.77–1.88 (m, 1H), 2.25 (s, 3H), 2.30–2.38 (m, 1H), 2.40 (s, 3H), 2.93–2.99 (m, 1H), 6.08 (s, 1H), 7.37 (d, J = 3.3 Hz, 1H), 8.17 (br s, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 11.3, 11.5, 19.1, 24.3, 28.0, 37.6, 49.7, 95.9, 119.1, 123.9, 124.7, 125.4, 156.1, 176.3, 194.7;

HRMS-ESI-TOF *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{20}NO_3$, 262.1438; found 262.1437.

1-(5-(((3*S*,4*S*)-4-Ethyl-3-methyl-5-methylenedihydrofuran-2(3*H*)-ylidene)methyl)-4-methyl-1*H*-pyrrol-3-yl)ethan-1-one (18). Preparation of the Petasis reagent and application here were conducted according to a standard procedure[4] with modifications. A solution of Cp_2TiCl_2 (4.59 g, 18.4 mmol) in anhydrous toluene (49 mL) at 0 °C under argon was treated dropwise with MeLi (1.6 M in Et_2O, 25 mL, 40 mmol). The reaction mixture was stirred at 0 °C for 1 h, and then saturated aqueous NH_4Cl (55 mL) was added. The organic layer was washed with water and brine, dried (Na_2SO_4) and filtered. The filtrate (containing the Petasis reagent) was treated with **17** (1.02 g, 3.9 mmol) and additional Cp_2TiCl_2 (58.2 mg). The reaction mixture was heated in an oil bath at 80 °C for 10 h in the dark under argon. The resulting mixture was diluted with CH_2Cl_2 and then filtered through Celite. The filtrate (clear reddish black) was concentrated and chromatographed [deactivated silica prepared by pretreating with hexanes containing 1% Et_3N, eluted with hexanes/ethyl acetate (1 : 1) containing 1% Et_3N, TLC R_f = 0.40] to yield a reddish dark paste (155.6 mg, 15%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.97 (t, J = 7.4 Hz, 3H), 1.08 (d, J = 7.1 Hz, 3H), 1.49–1.56 (m, 2H), 2.24 (s, 3H), 2.32–2.35 (m, 1H), 2.39 (s, 3H), 2.70–2.75 (m, 1H), 4.06 (dd, J = 2.1, 1.0 Hz, 1H), 4.51 (s, 1H), 5.78 (s, 1H), 7.33 (d, J = 3.2 Hz, 1H), 8.16 (br s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 11.3, 11.4, 19.4, 27.3, 27.9, 39.7, 50.4, 84.1, 90.3, 117.7, 124.4, 124.8, 125.8, 161.7, 162.9, 194.6; HRMS-ESI-TOF *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{22}NO_2$, 260.1645; found 260.1644.

(2*S*,3*S*)-8-Acetyl-2-ethyl-2,3-dihydro-1,3,7-trimethyldipyrrin (19). Following a general procedure[4] with some modifications, aqueous 1 M HCl (366 μL) was added to a solution of **18** (155.6 mg, 0.60 mmol) in DMF (7.1 mL). The reaction mixture was stirred at room temperature for 30 min. Afterward, NH_4OAc (0.94 g, 12.2 mmol) and Et_3N (1.7 mL, 12.2 mmol) were added, and the resulting solution was stirred in an oil bath at 55 °C for 10 min. The reaction mixture was rapidly cooled in an ice bath at 0 °C before being quenched and diluted by sequential addition of a cold saturated aqueous KH_2PO_4 solution (16 mL) and ethyl acetate (16 mL). The organic layer was washed with water, dried (Na_2SO_4), concentrated and chromatographed [deactivated silica prepared by pretreating with hexanes containing 1% Et_3N, eluted with hexanes/ethyl acetate (1 : 1) containing 1% Et_3N] to afford a brown paste (86.7 mg, 56%). TLC R_f 0.61 [silica, hexanes/ethyl acetate (1 : 2)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.94 (t, J = 7.4 Hz, 3H), 1.21 (d, J = 7.0 Hz, 3H), 1.38–1.46 (m, 1H), 1.72–1.81 (m, 1H), 2.17 (s, 3H), 2.31–2.33 (m, 1H), 2.35 (s, 3H), 2.39 (s, 3H), 2.62–2.67 (m, 1H), 5.80 (s, 1H), 7.37 (d, J = 3.2 Hz, 1H), 11.22 (br s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 10.8, 11.2, 19.0, 21.3, 24.5, 27.9, 40.8, 59.4, 102.5, 117.6, 124.3, 125.2, 130.0, 157.1, 182.0, 194.6; HRMS-ESI-TOF *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{23}N_2O$, 259.1805; found 259.1807.

(2*S*,3*S*)-8-Acetyl-2-ethyl-1-formyl-2,3-dihydro-3,7-dimethyldipyrrin (1b). Following a general procedure[4] with some modification, SeO_2 (0.11 g, 0.99 mmol) was added in one portion to a solution of **19** (86.7 mg, 0.336 mmol) in distilled 1,4-dioxane (10 mL) in the presence of added deionized water (16 μL). The reaction mixture was stirred at room temperature for 15 min. Ethyl acetate (12 mL) and saturated aqueous $NaHCO_3$ (12 mL) were added. The organic layer was washed with water, dried (Na_2SO_4), concentrated, and chromatographed [deactivated silica prepared by pretreating with hexanes containing 1% Et_3N, eluted with hexanes/ethyl acetate (1 : 1) containing 1% Et_3N] to afford a brown paste (9.3 mg, 10%). TLC R_f 0.67 [silica, hexanes/ethyl acetate (1 : 2)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, J = 7.4 Hz, 3H), 1.22 (d, J = 7.0 Hz, 3H), 1.42–1.50 (m, 1H), 1.82–1.90 (m, 1H), 2.41 (s, 3H), 2.42 (s, 3H), 2.75–2.78 (m, 2H), 6.28 (s, 1H), 7.49 (d, J = 3.3 Hz, 1H), 9.97 (s, 1H), 10.85 (br s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 11.0, 11.2, 21.9, 24.7, 28.1, 41.7, 53.9, 112.8, 122.9, 124.9, 127.6, 129.6, 156.8, 173.6, 190.2, 194.3; HRMS-ESI-TOF *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{21}N_2O_2$, 273.1598; found 273.1599.

Synthesis of enones

2-Carbomethoxy-3-[(2*S*,3*S*)-8-carboethoxy-2-ethyl-3-methyl-2,3-dihydrodipyrrin-1-yl]-1-[1-(1,1-dimethoxymethyl)-3,3,7-trimethyl-2,3-dihydrodipyrrin-8-yl]prop-2-en-1-one (3ab). Following a procedure[3] with some modification, solutions of the two dihydrodipyrrins corresponding to the stated quantities of **2b** (49.9 mg, 138 μmol) and (2*S*,3*S*)-8-carboethoxy-2-ethyl-1-formyl-3-methyl-2,3-dihydrodipyrrin (**1a**, 39.9 mg, 138 μmol) were added to a vial and concentrated to dryness, whereupon molecular sieves powder (3 Å, 50 mg) was added. The mixture was then treated with a solution of piperidine/acetic acid in acetonitrile (15 mM/15 mM, 3.50 mL, 52.5 μmol/52.5 μmol). The resulting mixture was stirred at room temperature for 60 h. Then the mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure and chromatographed [silica, hexanes/ethyl acetate (1 : 1), TLC R_f = 0.45] to afford an orange solid (30 mg, 34%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93 (t, J = 7.5 Hz, 3H), 1.11 (d, J = 10 Hz, 3H), 1.22 (s, 3H), 1.23 (s, 3H), 1.31 (t, J = 10 Hz, 3H), 1.36–1.45 (m, 1H), 1.74–1.82 (m, 1H), 2.41 (s, 3H), 2.46–2.49 (m, 1H), 2.56–2.59 (m, 1H), 2.62 (s, 2H), 3.41 (s, 6H), 3.77 (s, 3H), 4.24 (q, J = 7.1 Hz, 2H), 4.98 (s, 1H), 5.85 (s, 1H), 5.88 (s, 1H), 6.45 (s, 1H), 7.24 (d, J = 3.3 Hz, 1H), 7.32 (br, 1H), 7.40 (s, 1H), 10.26 (br, 1H), 11.14 (s, 1H)); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 10.9, 11.2, 14.7, 21.3, 25.3, 29.2, 29.3, 40.5, 40.7, 48.6, 53.0, 54.57, 54.60, 58.3, 59.6, 102.4, 103.9, 110.4, 110.9, 116.4, 118.8, 123.3, 126.4, 127.8, 130.4, 131.4, 131.6, 139.2, 157.3, 161.6, 165.2, 165.4, 172.6, 176.0, 189.2; HRMS-ESI-TOF *m*/*z*: $[M + H]^+$ calcd for $C_{35}H_{45}N_4O_7$ 633.3283; found 633.3285. λ_{abs} = 454 nm in toluene.

2-Carbomethoxy-3-[(2*S*,3*S*)-8-acetyl-2-ethyl-3,7-dimethyl-2,3-dihydrodipyrrin-1-yl]-1-[1-(1,1-dimethoxymethyl)-3,3,7-trimethyl-2,3-dihydrodipyrrin-8-yl]prop-2-en-1-one (3bb). Following a procedure[3] with some modification, solutions of the two dihydrodipyrrins corresponding to the stated quantities of **1b** (9.3 mg, 34 μmol) and **2b** (12.2 mg, 33.7 μmol) were added to a vial and concentrated to dryness, whereupon molecular sieves powder (3 Å, 13 mg) was added. The mixture was then treated with a solution of piperidine/acetic acid in acetonitrile (15 mM/15 mM, 0.8 mL, 12.0 μmol/12.0 μmol). The resulting mixture was stirred at room temperature for 20 h, and then filtered through a Celite pad. The filtrate was concentrated under reduced pressure and

chromatographed [silica, hexanes/ethyl acetate (1 : 1), TLC R_f = 0.48] to afford an orange paste (2.0 mg, 10%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93 (t, J = 7.4 Hz, 3H), 1.14 (d, J = 7.1 Hz, 3H), 1.22 (s, 6H), 1.37–1.47 (m, 1H), 1.75–1.80 (m, 1H), 2.29 (s, 3H), 2.32 (s, 3H), 2.43 (s, 3H), 2.46–2.50 (m, 1H), 2.60–2.63 (m, 3H), 3.41 (s, 6H), 3.77 (s, 3H), 4.98 (s, 1H), 5.89 (s, 1H), 5.92 (s, 1H), 7.22 (s, 1H), 7.26 (s, 1H, overlapped by residual solvent peak), 7.40 (s, 1H) 10.32 (br s, 1H), 11.15 (br s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ 10.8, 10.9, 11.2, 21.5, 25.3, 27.9, 29.27, 29.32, 40.5, 41.0, 48.7, 53.0, 54.61, 54.63, 58.2, 102.4, 103.8, 107.9, 118.8, 120.3, 123.4, 124.1, 127.5, 127.9, 129.7, 130.4, 131.5, 139.0, 156.9, 161.7, 165.4, 172.2, 176.2, 194.3, one quaternary carbon (aromatic region) is missing; HRMS-ESI-TOF m/z: $[M + H]^+$ calcd for $C_{35}H_{45}N_4O_6$ 617.3334; found 617.3344. λ_{abs} = 485 nm in toluene.

Synthesis of bacteriochlorophyll analogues

(17*S*,18*S*)-3-Carboethoxy-13^2-carbomethoxy-17-ethyl-8,8,12,18-tetramethyl-13^1-oxobacteriophorbine (BC-ab). Following a literature procedure[3] with modification, a mixture of **3ab** (20 mg, 32 μmol) and Yb(OTf)$_3$ (198 mg, 320 μmol) in acetonitrile (160 mL) under an argon atmosphere in a glovebox was stirred at 80 °C (internal temperature) for 4 h. The reaction flask was allowed to cool to room temperature and then evacuated from the glovebox. The resulting mixture was concentrated under reduced pressure followed by chromatography [silica, hexanes/ethyl acetate (2 : 1)] to afford two purple bands.

Band 1, the decarbomethoxylated by-product **BC-ab-pyro** (0.2 mg, 1.2%): ^{1}H NMR (500 MHz, $CDCl_3$) δ −1.43 (br, 1H), −0.28 (br, 1H), 1.01 (t, J = 7.3 Hz, 3H), 1.67 (t, J = 7.1 Hz, 3H), 1.76 (d, J = 7.4 Hz, 3H), 1.91 (s, 3H), 1.95 (s, 3H), 1.98–2.07 (m, 1H), 2.28–2.35 (m, 1H), 3.53 (s, 3H), 4.09–4.12 (m, 1H), 4.35–4.41 (m, 3H), 4.72–4.76 (m, 2H), 5.01 (d, J = 19.6 Hz, 1H), 5.14 (d, J = 19.7 Hz, 1H), 8.52 (s, 1H), 8.56 (s, 1H), 9.19 (s, 1H), 9.69 (s, 1H); HRMS-ESI-TOF m/z: $[M + H]^+$ calcd for $C_{31}H_{35}N_4O_3$ 511.2704; found 511.2692. λ_{abs} = 757 nm, λ_{em} = 760 nm, Φ_f = 0.17 (λ_{ex} = 536 nm), in toluene.

Band 2, **BC-ab** comprising two epimers in 10 : 1 ratio (R_f 0.35 in hexanes/ethyl acetate (2 : 1), 12.2 mg, 67%). The following data are for the major epimer: ^{1}H NMR (500 MHz, $CDCl_3$) δ −1.39 (br, 1H), −0.20 (br, 1H), 0.99 (t, J = 7.3 Hz, 3H), 1.67 (t, J = 7.2 Hz, 3H), 1.76 (d, J = 7.3 Hz, 3H), 1.91 (s, 3H), 1.95 (s, 3H), 1.98–2.04 (m, 1H), 2.29–2.35 (m, 1H), 3.55 (s, 3H), 3.85 (s, 3H), 3.96–3.99 (m, 1H), 4.32–4.37 (m, 1H), 4.41 (s, 2H), 4.70–4.79 (m, 2H), 6.15 (s, 1H), 8.55 (s, 1H), 8.56 (s, 1H), 9.21 (s, 1H), 9.70 (s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 10.8, 11.9, 14.8, 23.2, 27.7, 31.2, 31.3, 45.2, 49.0, 52.8, 53.0, 53.7, 61.3, 64.9, 97.3, 99.0, 100.2, 107.9, 123.4, 124.9, 129.0, 129.6, 136.2, 136.4, 140.4, 148.0, 160.6, 163.0, 165.2, 169.5, 169.7, 171.5, 189.7; HRMS-ESI-TOF m/z: $[M + H]^+$ calcd for $C_{33}H_{37}N_4O_3$ 569.2758; found 569.2764. λ_{abs} = 759 nm, λ_{em} = 762 nm, Φ_f = 0.16 (λ_{ex} = 533 nm), in toluene.

(17*S*,18*S*)-3-Acetyl-13^2-carbomethoxy-17-ethyl-2,8,8,12,18-hexamethyl-13^1-oxobacteriophorbine (BC-bb). Following a literature procedure[3] with modification, a mixture of **3bb** (2.0 mg, 3.2 μmol) and Yb(OTf)$_3$ (19.8 mg, 32 μmol) in acetonitrile (16 mL) under an argon atmosphere in a glovebox was stirred at 80 °C (internal temperature) for 4 h. Upon completion, the reaction flask was allowed to cool to room temperature and then evacuated from the glovebox. The resulting mixture was concentrated under reduced pressure followed by chromatography [silica, hexanes/ethyl acetate (1 : 1), TLC R_f = 0.45] to afford a purple band (0.75 mg, 42%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ −0.79 (br s, 1H), 0.60 (br s, 1H), 0.98 (t, J = 7.3 Hz, 3H), 1.72 (d, J = 7.3 Hz, 3H), 1.86 (s, 3H), 1.89 (s, 3H), 1.94–2.00 (m, 1H), 2.24–2.29 (m, 1H), 3.14 (s, 3H), 3.45 (s, 3H), 3.48 (s, 3H), 3.84 (s, 3H), 3.87–3.90 (m, 1H), 4.25–4.30 (m, 3H), 6.03 (s, 1H), 8.34 (s, 1H), 8.39 (s, 1H), 8.93 (s, 1H); HRMS-ESI-TOF m/z: $[M + H]^+$ calcd for $C_{33}H_{37}N_4O_4$ 553.2809; found 553.2806.

Streamlined synthesis of BC-bb. Following a procedure[3] with some modification, solutions containing **1b** (10.1 mg, 37 μmol) and **2b** (13.4 mg, 37 μmol) were added to a vial and concentrated to dryness, whereupon molecular sieves powder (3 Å, 13.4 mg) was added. The mixture was then treated with a solution of piperidine/acetic acid in acetonitrile (15 mM/15 mM, 0.93 mL, 14.0 μmol/14.0 μmol). The resulting mixture was stirred at room temperature for 20 h, and then filtered through a Celite pad. The filtrate was concentrated under reduced pressure. Chromatography of the resulting residue [silica, hexanes/ethyl acetate (1 : 1)] afforded a fraction containing **3bb** (10.2 mg). The sample in its entirety was dissolved in $CDCl_3$ with added mesitylene (2.0 μL, 14 μmol) as an internal standard to obtain a clear solution. Analysis by ^{1}H NMR spectroscopy showed the presence of **3bb** in purity of 20% (corresponding to 3.1 μmol of the desired enone); the main contaminants were unreacted **2b** and an unknown species. The molar ratio of **3bb**:mesitylene was calculated by comparison of the integration of the singlet at δ 5.92 ppm (one methine proton at a *meso*-position in **3bb**) and the singlet at δ 6.80 (three aromatic protons in mesitylene). The entire sample was recovered, concentrated, and dried under high vacuum. The resulting residue was treated with Yb(OTf)$_3$ (19.2 mg, 31 μmol) in acetonitrile (15.5 mL) under argon in a glovebox. The reaction mixture was stirred at 80 °C (internal temperature) for 4 h, then allowed to cool to room temperature before removal from the glovebox. The resulting mixture was then concentrated and chromatographed [silica, hexanes/ethyl acetate (1 : 1), TLC R_f = 0.45] to give a purple residue (0.91 mg, 53% yield based on the 3.1 μmol quantity in the crude starting material). ^{1}H NMR ($CDCl_3$, 700 MHz) δ −0.79 (br s, 1H), 0.60 (br s, 1H), 0.98 (t, J = 7.3 Hz, 3H), 1.72 (d, J = 7.4 Hz, 3H), 1.86 (s, 3H), 1.89 (s, 3H), 1.94–2.00 (m, 1H), 2.23–2.29 (m, 1H), 3.14 (s, 3H), 3.45 (s, 3H), 3.48 (s, 3H), 3.84 (s, 3H), 3.87–3.89 (m, 1H), 4.25–4.29 (m, 3H), 6.03 (s, 1H), 8.34 (s, 1H), 8.39 (s, 1H), 8.93 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 175 MHz) δ 10.8, 11.7, 13.6, 23.1, 27.7, 31.2, 31.3, 33.4, 44.6, 49.7, 52.9, 53.0, 53.4, 64.7, 96.0, 97.5, 98.0, 108.3, 121.2, 128.7, 133.5, 136.39, 136.44, 138.6, 139.3, 148.4, 159.2, 164.2, 169.8, 170.0, 170.6, 189.4, 199.4; HRMS-ESI-TOF m/z: $[M + H]^+$ calcd for $C_{33}H_{37}N_4O_4$ 553.2809; found 553.2804. λ_{abs} = 758 nm, λ_{em} = 768 nm, Φ_f = 0.13 (λ_{ex} = 531 nm), in toluene.

Macrocycle formation – comparison of rates

The reaction of **3ab** was carried out exactly as for that of **3aa-*E*** reported earlier.[6] Briefly, the reaction of **3ab** was carried out in

a closed and stirred 4 mL conical vial placed in a temperature-controlled aluminum block located inside a glove box containing an argon atmosphere. Because of good heat transfer and the small volume of solvent, the (internal) solvent temperature was nearly identical to the (external) block temperature, which was set at 80 or 50 °C; the internal temperature was confirmed by occasionally checking with a glass thermometer at the end of the reaction. The temperatures for the reactions shown in Fig. 2 are the internal temperatures (the solvent inside the vial). Samples were removed periodically for analysis by absorption spectroscopy to assess the reaction course and the yield of **BC-ab** using the molar absorption coefficient of **BC-aa** (ε = 72 100 M^{-1} cm^{-1} for the Q_y band). The analysis method also was identical to that reported earlier.[6]

Fluorescence spectroscopy

Instrumental parameters used to record emission spectra and determine the quantum yields were as follows: excitation and emission slit width = 1.5 nm (0.375 mm); photomultiplier tube (Hamamatsu R928P) voltage = 1000; and integration time = 1 nm s^{-1}. For all emission spectra, instrumental sensitivity was corrected as a function of wavelength. Fluorescence quantum yields were determined relative to the known standard 2,12-di-*p*-tolyl-8,8,18,18-tetramethylbacteriochlorin (Φ_f = 0.18, toluene).[49]

Conflicts of interest

The authors declare the following competing financial interest(s): J. S. L. is a cofounder of NIRvana Sciences, which has licensed aspects of technology antecedent to that described herein.

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