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Use of the Nascent Isocyclic Ring to Anchor Assembly of the Full Skeleton of Model Chlorophylls

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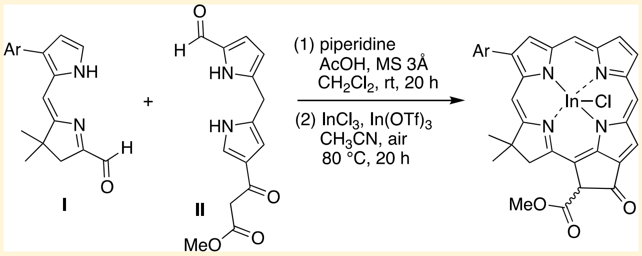
Supporting Information



ABSTRACT: The chlorophyll skeleton contains a chlorin macrocycle and an annulated fifth (or isocyclic) ring bearing 13^1-oxo and 13^2-carbomethoxy substituents. The isocyclic ring has traditionally been constructed by annulation of an intact tetrapyrrole macrocycle. Here, a complementary route employs reaction of a gem-dimethyl-substituted dihydrodipyrrin−carboxaldehyde (AD half) and a dipyrromethane bearing a 3-methoxy-1,3-dioxopropyl group (BC half). A McMurry-like reaction of a 2-(2-nitro-5-oxohexyl)pyrrole was employed to construct the second pyrrole ring in one of three BC halves, whereas the other two were prepared by known routes. An AD half and a BC half were joined by Knoevenagel condensation at room temperature, affording the AD,BC-substituted 2-methoxycarbonyl-2-propenone. The subsequent reaction of three AD, BC-propenones (mixture of *Z*,*E*-isomers) in CH_3CN containing $InCl_3$ and $In(OTf)_3$ at 80 °C afforded the chlorophyll skeleton as the chloroindium(III) chelate; the reaction proceeds via Nazarov cyclization (to form the isocyclic ring), S_EAr (to construct the macrocycle), and $2e^-,2H^+$ oxidation (to give the aromatic chromophore). The absorption spectra of the complexes closely resemble that of chlorophyll *a*. The present work exploits the nascent isocyclic ring as an anchor for directed assembly of the AD and BC halves, forming both the chlorin macrocycle and the isocyclic ring in a single-flask transformation.

INTRODUCTION

New routes to chlorophylls and close analogues thereof may provide the foundation for addressing scientific questions that arise in both natural and artificial photosynthesis. The skeleton of all chlorophylls—a phorbine—is a tetrapyrrole macrocycle containing one reduced pyrrole ring (chlorin) and an annulated five-membered ring (the isocyclic ring); the latter carries an oxo group at the 13^1-position (affording a 13^1-oxophorbine). Chlorophylls from plants and cyanobacteria also contain a carbomethoxy group at the 13^2-position, resulting in a *β*-ketoester motif. The structures of the most prevalent such macrocycles,[1] chlorophyll *a* and chlorophyll *b*, are shown in Chart 1 along with the core chlorin and phorbine structures.

Numerous routes have been developed for the synthesis of chlorins over the past century,[2−4] yet relatively few routes provide for installation of the isocyclic ring. Indeed, the vast majority of studies with synthetic chlorophyll analogues rely on chlorin macrocycles alone rather than the more biomimetic 13^2-carbomethoxy-13^1-oxophorbines. Three distinct routes are shown in Scheme 1.[2] (1) Dieckmann cyclization of chlorin e_6 trimethyl ester (**Chl-e_6 Me$_3$**) affords methyl pheophorbide *a* (**Me-Pheo *a***) in the presence of bases such as KOH/pyridine,[5] NaOMe in methanol/acetone,[6] potassium *tert*-butoxide/pyridine,[7−9] PPh_3/sodium bis(trimethylsilylamide),[10] or potassium *tert*-butoxide/collidine.[11] (2) Cyclization of a *β*-ketoester attached to the 13-position of a chlorin (**pre Me-Pheo *a***) with the adjacent 15-position also affords the isocyclic ring (**Me-Pheo *a***),[12−15] most recently with 2 equiv of thallium trifluoroacetate followed by photolysis and then thallium demetalation (SO_2/aqueous HCl) on workup.[16] (3) Stille coupling of a 13-bromochlorin (**C-Br**) to install a 13-acetyl group, 15-bromination, and Pd-catalyzed *α*-arylation of the resulting chlorin (**C-Ac**) affords the 13^1-oxophorbine (**Oxo-Phorb**), but does not accommodate the 13^2-ester moiety.[17,18]

In each of the above cases, the isocyclic ring is installed by late-stage derivatization of an intact chlorin. Recently, a de novo route constructs the bacteriochlorin macrocycle as well as the isocyclic ring in a one-flask reaction (Scheme 2).[19] Knoevenagel condensation of two dihydrodipyrrins (**I** and **II-BC**) affords enone **III-BC**. Subsequent double ring-closure of **III-BC** (by Nazarov reaction and electrophilic aromatic substitution) followed by elimination of methanol yields the bacterio-13^1-oxophorbine skeleton, which bears the 13^2-carboalkoxy group characteristic of native bacteriochlorophylls.

The success of the de novo synthesis of the bacteriochlorophyll skeleton suggests direct extension to the skeleton of chlorophylls, yet there are significant differences in the two types of chromophores. First, bacteriochlorins contain two pyrroline rings whereas chlorins contain only one; hence, both reactants in bacteriochlorins are dihydrodipyrrins whereas in chlorins one is a dihydrodipyrrin and the other is a dipyrromethane (or dipyrrin). Second, dipyrromethanes and dipyrrins are valuable building blocks but are not without

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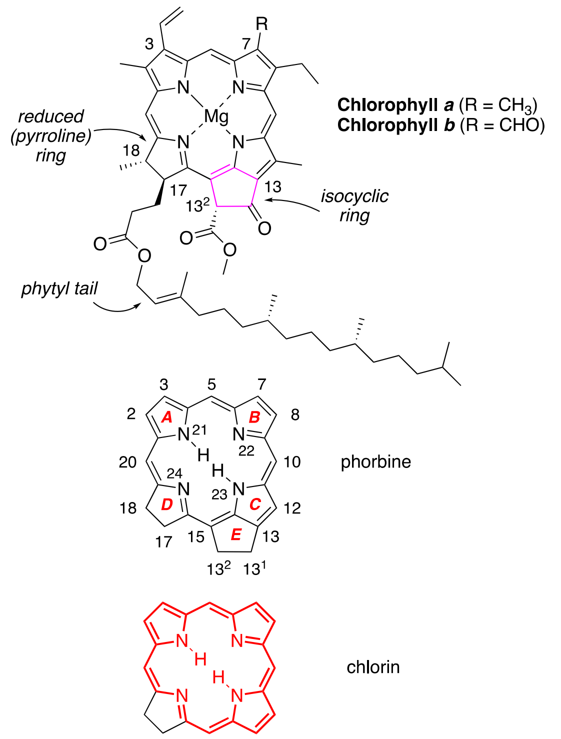
Chart 1. Structures of Chlorophylls *a* and *b*, the Phorbine Macrocycle, and the Core Chlorin



constraints: (a) dipyrromethanes often[20,21] (but not always[22]) can be employed in Pd-mediated coupling reactions, but are inherently susceptible to acidolytic scrambling;[23] (b) free base dipyrrins thwart Pd-mediated coupling reactions[24] but do not undergo acidolysis; and (c) dipyrromethanes are far more reactive than dipyrrins at the α-positions toward electrophilic substitution. Third, neither dipyrromethanes nor dipyrrins analogous to dihydrodipyrrin **II-BC** have heretofore been prepared.

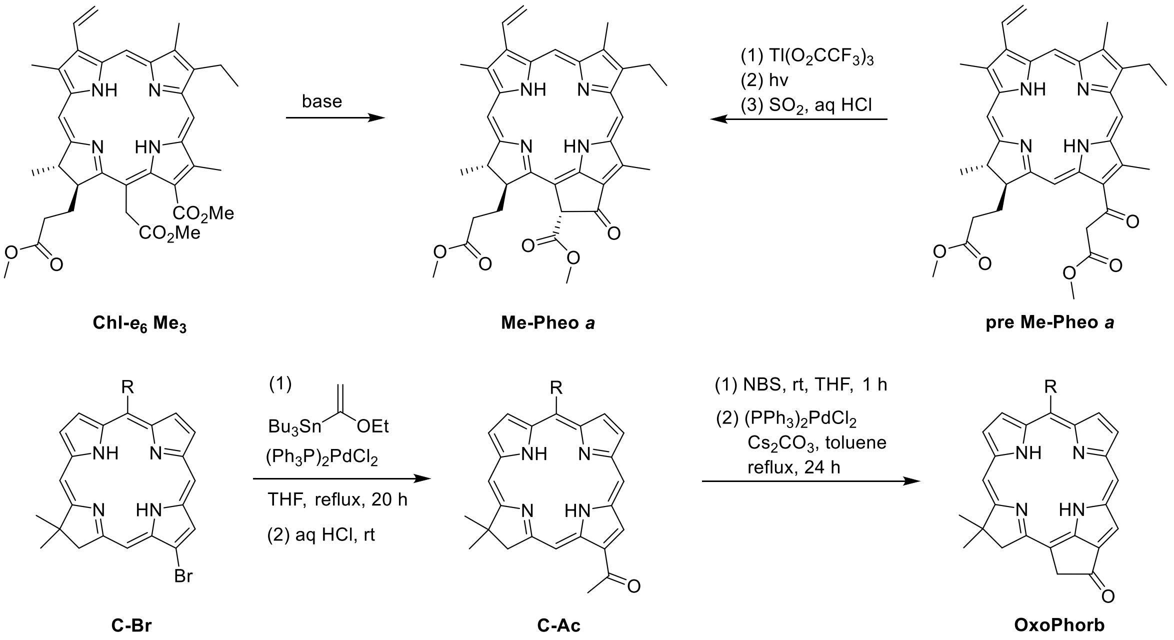
In this paper, we report the synthesis of dipyrromethanes for application in a de novo synthesis of the skeleton of model chlorophylls. The dipyrromethanes bear a 9-formyl group (rather than an acetal as in **II-BC**), a 2-(1,3-dioxo-3-methoxypropyl) motif, and (optionally) a 5-aryl group. The dihydrodipyrrins employed resemble **I**, wherein a gem-dimethyl group stabilizes the pyrroline ring toward adventitious oxidation. Subsequent studies will focus on accommodating stereochemically defined trans-dialkyl substituents in ring D. The research marks one step toward the long-term objective[25] of achieving workable syntheses of the native chlorophyll and bacteriochlorophyll pigments.

■ RESULTS AND DISCUSSION

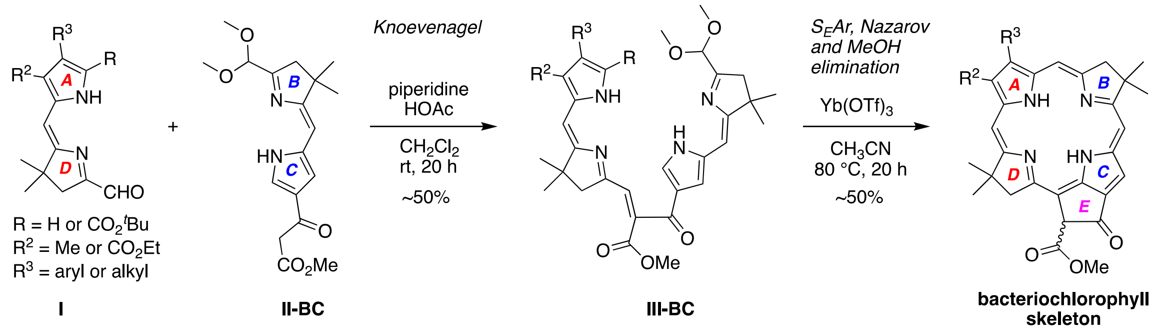
1. Synthesis of BC Halves. *1.1. Dipyrromethane without a meso-Substituent.* Dipyrromethane **1**, which bears 1-carboxaldehyde and 8-bromo substituents, has been prepared via a stepwise route.[26] Attempts to install the β-ketoester functionality on **1** via Pd-mediated coupling were unsuccessful. Accordingly, we turned to *N*-Boc protection to mask the N−H units. Treatment of **1** to the standard conditions for Boc derivatization[27] (with di-*tert*-butyl dicarbonate (4.0 equiv) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP, 0.2 equiv)) afforded the *N*-protected dipyrromethane **(Boc)$_2$-1** in 95% yield. Carbonylation[19] of **(Boc)$_2$-1** with methyl potassium malonate and $Co_2(CO)_8$ in the presence of $Pd(OAc)_2$/Xantphos afforded the methyl-substituted β-ketoester dipyrromethane **(Boc)$_2$-2** in 57% yield. The *N*-Boc groups were cleaved by treatment with TFA/CH_2Cl_2 (1:2), giving dipyrromethane **2** in 69% yield (Scheme 3).

We also sought the analogue bearing an acetal instead of a carboxaldehyde group so as to resemble the BC half (**II-BC**) in bacteriochlorin formation. The proposed synthesis of the dipyrromethane−acetal started from the known pyrrole **4**[28] and 1,1-dimethoxybut-3-en-2-one[29] (**3a**). The Michael addition of a dimethyl-substituted analogue of **3a** (**3b**, R = Me) with **4** has been employed extensively[19,28] and found to

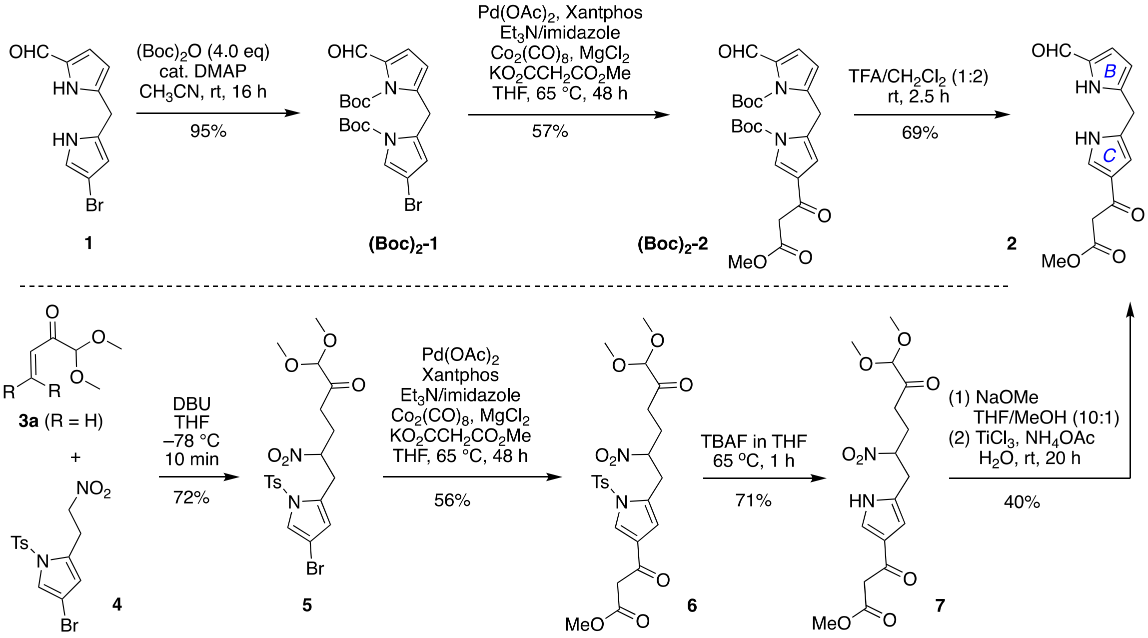
Scheme 1. Installation of the Isocyclic Ring on Intact Chlorins



Scheme 2. De Novo Synthesis of the Skeleton of Bacteriochlorophylls



Scheme 3. Two Synthesis Pathways to BC Half 2



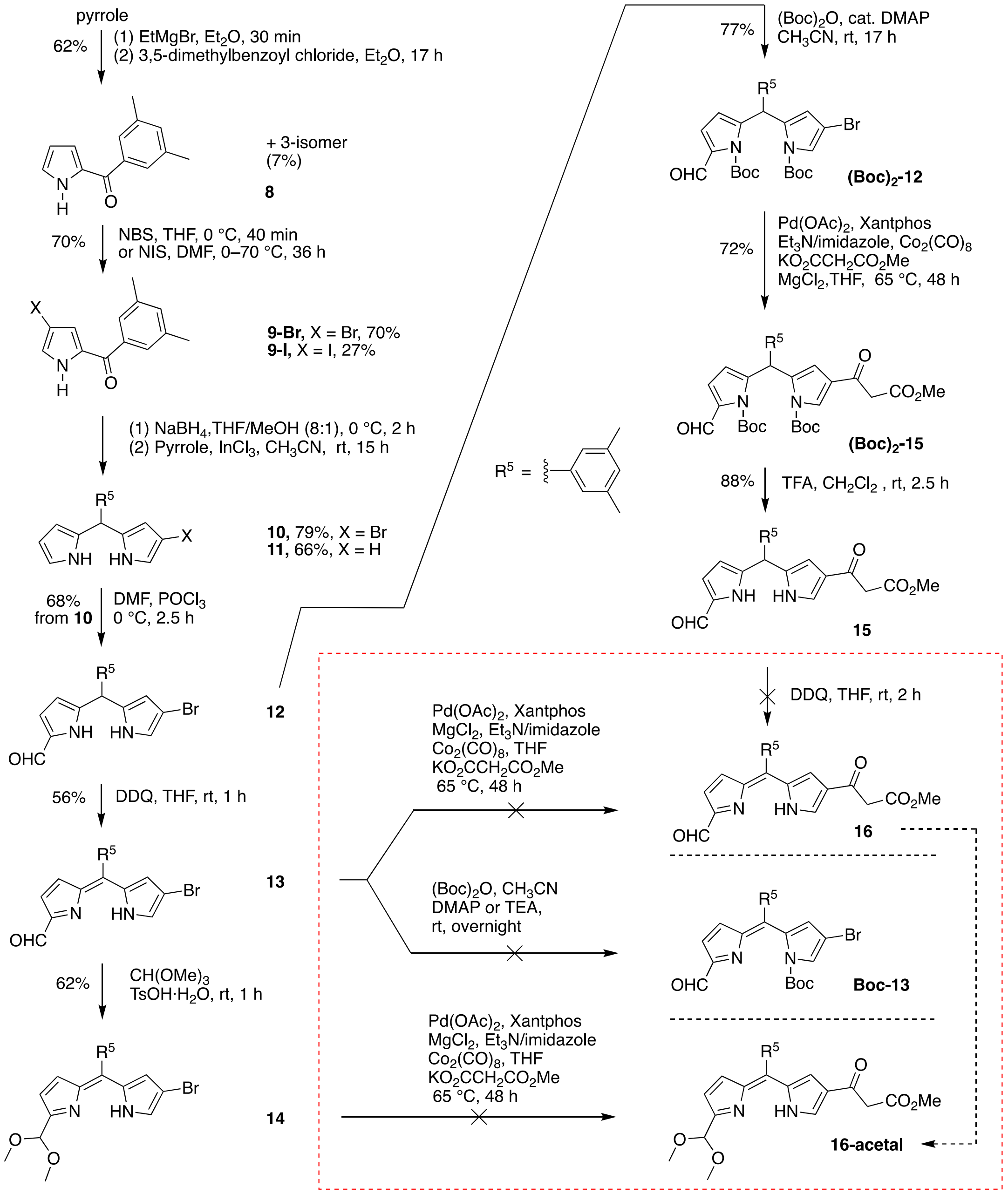
proceed at room temperature in the presence of neat DBU. Similar treatment of **3a** and **4** did not give the desired product. Ultimately, a lower temperature (−78 °C rather than rt), lower concentration (0.02 M in tetrahydrofuran (THF) rather than neat), and fewer equivalents (1.1 vs 3.0) of the acceptor afforded **5** in 72% yield. The greater reactivity of **3a** (R = H) versus **3b** (R = Me) coheres with recent evaluations of the electrophilicity of Michael acceptors, where a single methyl group at the *β*-position can alter the rate by a factor of 250-fold.[30]

Treatment of **5** under standard conditions[19] for installation of the *β*-ketoester gave **6** in 56% yield. Removal of the tosyl group in **6** by refluxing in THF containing TBAF gave the free pyrrole **7** in 71% yield. Afterward, **7** was treated with NaOMe followed by a buffered aqueous-organic solution[31] of $TiCl_3$ for 20 h at room temperature to afford dipyrromethane **2** in 40% yield. Unexpectedly, the acetal group was hydrolyzed to give the formyl group, most likely facilitated by the electron-rich nature of the adjacent pyrrole. The single-crystal X-ray structure of **2** (derived from **3a** + **4**) is provided in the Supporting Information. The dominant process for synthesizing dipyrromethanes relies on joining intact pyrroles[32−34] and is complemented here by the stepwise construction of a second pyrrole from the substituents attached to a first pyrrole. The overall yield from **1** to **2** is 37% in 3 steps versus 11% from **3a** and **4** in 4 steps; the difference in yield must be balanced against the more facile access to **3a** and **4** compared with **1**.

Dipyrromethanes have an Achilles heel—acidolytic cleavage that engenders the notorious problem of "scrambling".[23] A workaround is to employ a dipyrrin[35] as the BC half because dipyrrins do not undergo acidolysis. Attempts to dehydrogenate dipyrromethane **1** via the standard conditions of DDQ or *p*-chloranil[24] or with copper(II)[36] were unsuccessful in affording the corresponding dipyrrin. Dehydrogenation with DDQ or *p*-chloranil in the presence of Zn(II), Pd(II), or Cu(II) to obtain the bis(dipyrrinato)metal complex also was unsuccessful (see the Supporting Information). Successful dehydrogenations of dipyrromethanes typically have been carried out for substrates bearing an aryl group at the meso-position (or multiple *β*-pyrrole groups), but not deactivating groups such as the *α*-carboxaldehyde. The failure here prompted the pursuit of an analogue of **2** that bears a meso-aryl group.

1.2. Dipyrromethane with a meso-Aryl Substituent. Treatment[26] of pyrrole with EtMgBr followed by 3,5-dimethylbenzoyl chloride afforded the *α*-aroylated pyrrole **8** in 62% yield (Scheme 4, left series). Bromination at the pyrrole 4-position was achieved in 70% yield. Iodination of **8** over a longer time (36 h) and higher temperature (70 °C) in dimethylformamide (DMF) afforded *β*-iodinated pyrrole **9-I** in

Scheme 4. Synthesis Route to Dipyrromethane 15

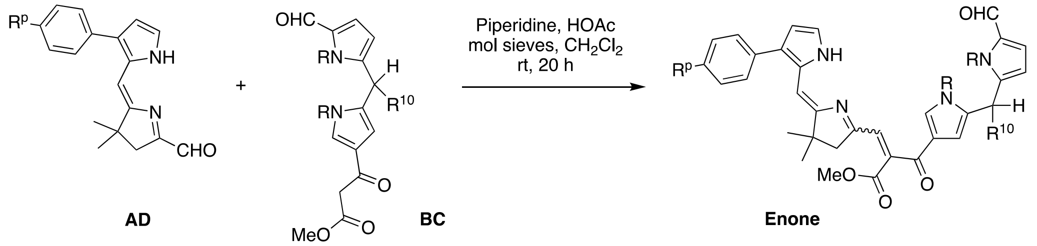


only 27% yield, albeit with substantial recovery (67%) of **8**. Attempts to increase the yield by carrying out the reaction in THF, $CHCl_3$, or MeCN gave only a trace amount of **9-I**. The single-crystal X-ray structures of **8** and **9-Br** are shown in the Supporting Information.

Reduction of **9-Br** gave the *α*-carbinol, which upon treatment with excess pyrrole in acid[26] gave dipyrromethane **10** in 79% yield. However, the dipyrromethane bearing a *β*-iodo atom (derived from **9-I**) afforded only the symmetric dipyrromethane **11**, in 66% yield. Vilsmeier formylation of **10** gave the corresponding dipyrromethane−carboxaldehyde **12** in 68% yield, where formylation occurred on the pyrrole ring lacking the bromo substituent. To prepare for installation of the *β*-ketoester functionality, treatment of **12** with di-*tert*-butyl dicarbonate and a catalytic amount of DMAP gave the *N*-Boc dipyrromethane **(Boc)$_2$-12** in 77% yield at ∼6 mmol scale. Subsequent *β*-ketoester introduction (as for preparation of **(Boc)$_2$-2**) gave **(Boc)$_2$-15** in 72% yield. Addition of TFA caused cleavage of the Boc groups to afford the free dipyrromethane **15** in 88% yield (Scheme 4, right series). Attempted dehydrogenation of **15** did not afford the desired target **16**, which is a 5-xylyl-substituted dipyrrin analogue of **2**. The failure to form **16** also closed the door to the desired final transformation, conversion of the carboxaldehyde to form the acetal of **16-acetal**.

Several other transformations were examined as possible entries to **16-acetal**. Dehydrogenation of dipyrromethane−carboxaldehyde **12** with DDQ afforded dipyrrin−carboxaldehyde **13** in 56% yield. Treatment of **13** with trimethyl orthoformate and *p*-toluenesulfonic acid[37] afforded the acetal **14** in 62% yield (Scheme 4). Attempts to install the *β*-ketoester with dipyrrins **13** and **14** were unsuccessful, which is not surprising given the coordinative avidity of dipyrrins for divalent metals.[35] Attempts to dehydrogenate **12** in the

Table 1. Knoevenagel Reaction of AD and BC Halves[a]



	compounds			substituents			
entry	AD[a]	BC[b]	enone	R^p	R	R^{10}	yield (%)
1	**17**	**2**	**19**	CH$_3$	H	H	51[c]
2	**18**	**2**	**20**	Br	H	H	34[c]
3	**17**	**(Boc)$_2$-2**	**(Boc)$_2$-19**	CH$_3$	CO$_2{}^t$Bu	H	64
4	**18**	**(Boc)$_2$-2**	**(Boc)$_2$-20**	Br	CO$_2{}^t$Bu	H	50
5	**18**	**15**	**21**	Br	H	*m*-xylyl[d]	44[c]

[a] AD half, a dihydrodipyrrin in each case. [b] BC half, a dipyrromethane in each case. [c] Yield of two isomers. [d] 3,5-Dimethylphenyl.

presence of a Pd(II) reagent, thereby forming the bis(dipyrrinato)Pd(II) species for use in subsequent Pd-mediated coupling reactions, also were unsuccessful (see the Supporting Information). Finally, attempts to install a blocking group (*N*-Boc) on the pyrrole-like unit of the dipyrrin also did not succeed.

In summary, while the dipyrrin bearing a *β*-ketoester at the pyrrole *β*-position (**16-acetal**)—as required for use as an acid-resistant BC-half—was not obtained, distinct reactivity was starkly revealed: 5-xylyldipyrromethane **12** was smoothly dehydrogenated to from 5-xylyldipyrrin **13**, whereas 5-xylyldipyrromethane **15** and 5-unsubstituted dipyrromethane **1** failed. Dehydrogenation of a dipyrromethane to a dipyrrin appears to benefit from if not require a meso-substituted aryl group, and can tolerate at most one attached carbonyl group, at least with the conditions examined here. The same reactivity distinction is mirrored in the ring-closure reaction leading to chlorins (vide infra).

2. Assembly of the AD and BC Halves. *2.1. Synthesis.* The Knoevenagel condensation of the known[19] AD halves **17** and **18** and the new BC halves **2** and **15** was carried out in the presence of piperidine/HOAc and powdered molecular sieves 3 Å in anhydrous CH$_2$Cl$_2$ under argon at room temperature, conditions developed in the bacteriochlorophyll-skeleton synthesis[19] (Scheme 2). The resulting Knoevenagel enones **19**, **20**, and **21** were obtained in 51, 34, and 44% yield, respectively (Table 1). Two isomers of **20** (17 mg, 2 mg; 8.5:1) and of **21** (15 mg, 2.4 mg; 6:1) could be separated using reversed-phase thin-layer chromatography (TLC) [R_f = 0.50, 0.40 in methanol/H$_2$O (8:1)] and preparative thin chromatography [R_f = 0.30, 0.25 in hexanes/ethyl acetate (3:2)] using a small portion of the overall material. On the other hand, the two isomers of **19** exhibited similar polarity on reversed-phase TLC [R_f = 0.46, 0.44 in methanol/H$_2$O (5:1)] and only the major isomer was isolated in pure form.

To possibly improve the yield, dipyrromethane **(Boc)$_2$-2** was employed as the BC half. Knoevenagel reaction with the AD half **17** or **18** gave the corresponding enone **(Boc)$_2$-19** or **(Boc)$_2$-20** in 64 or 50% yield, respectively, without apparent formation of isomers. At present, the slight increase in yield with **(Boc)$_2$-2** versus **2** alone does not appear to warrant the extra procedures required to install the Boc groups.

Each Knoevenagel enone was isolated as a red gum. The absorption spectra of all five products are shown in Figure 1.

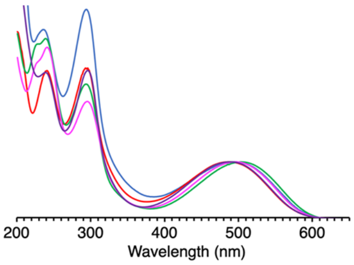


Figure 1. Absorption spectra of enones **19** (blue), **20** (red), **(Boc)$_2$-19** (green), **(Boc)$_2$-20** (magenta), and **21** (purple) in CH$_3$CN at room temperature (normalized at ~480 nm). The peak absorption in the visible region is at ~484 nm (**19**), ~487 nm (**20**), ~503 nm [**(Boc)$_2$-19**], ~497 nm [**(Boc)$_2$-20**], and ~488 nm (**21**).

The absorption band at ~300 nm likely stems from the presence of the pyrrole−carboxaldehyde moiety, given that 5-methylpyrrole-2-carboxaldehyde absorbs similarly at 306 nm (ε 13 500 M^{-1} cm^{-1}).[38] The absorption spectrum with accompanying molar absorption coefficient data for **20** (λ_{abs} (CH$_3$CN) at 487 nm = 1.3 × 10^4 M^{-1} cm^{-1}) is shown in the Supporting Information. The absorption spectra of the major and minor isomers of **20**, of **21**, and of the major isomer of **19**, were essentially identical with each other for the two peaks at wavelengths >260 nm.

2.2. Isomer Analysis. The ^{1}H NMR spectra of the isolated pair of enone isomers in each case were quite similar, with one distinction observed by the ring-B carboxaldehyde resonance. Two peaks of unequal intensity were discernible, with the dominant peak at higher field strength in each case; for example, a 6:1 ratio was observed for **19** (prior to separation of the isomers). For **20** and **21**, where major and minor isomers of each could be separated, the major isomer resonated at higher field strength: 9.31 vs 9.39 ppm (**20**) and 9.24 vs 9.41 ppm (**21**). A single resonance was observed for each of **(Boc)$_2$-19** and **(Boc)$_2$-20**, consistent with the single band observed by TLC analysis. To assign *Z* versus *E* enone isomers, we carried out 2D NOESY NMR analysis for the purified major constituent of **20**. The noteworthy correlations are displayed in Figure 2. The diagnostic correlations for

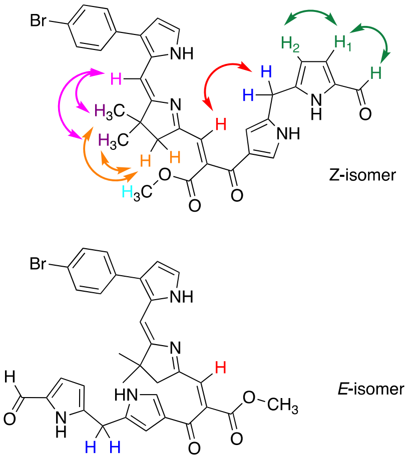
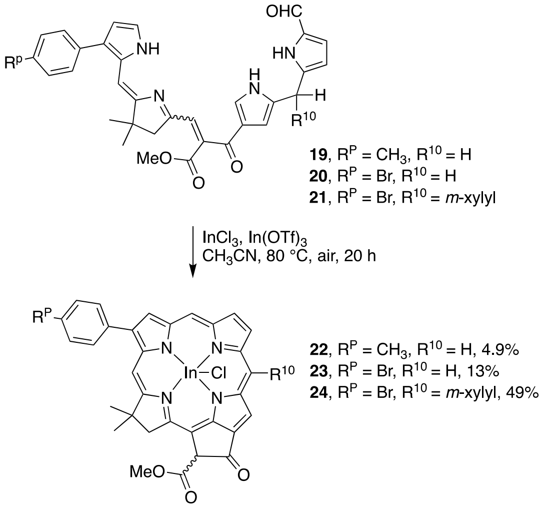


Figure 2. Arrows show the key correlations observed upon 2D NOESY NMR analysis of the major enone of **20**, which is assigned to the *Z*-isomer (top). The *E*-isomer is shown for comparison (bottom).

disambiguating the *Z* and *E* isomers emanate between the vinyl proton and the meso-protons of the dipyrromethane. The conformations of the *Z* and *E* isomers were assessed by energy minimization (MM2 of Chem3D) followed by distance measurements (PyMol). The NOESY diagram, molecular conformations, and distance measurements are provided in the Supporting Information. The distance between the vinyl proton (red) and the meso-protons (blue) ranges from 4.4−6.0 Å for the *Z* isomer but 7.7−8.0 Å for the *E* isomer. Accordingly, the major component is assigned to the *Z* isomer. Confirmation of this analysis requires study of the minor enone of **20**; however, limited quantity (2 mg) and poor solubility ($CDCl_3$, THF-d_8, and methanol-d_4) precluded 2D NOESY analysis despite extensive effort (a 20 h run with a 700 MHz NMR instrument). Analogous 2D NOESY studies on the separated isomers of **21** afforded weak signals and were inconclusive.

3. Formation of the Chlorophyll Skeleton. Enones **19**−**21**, **(Boc)$_2$-19**, and **(Boc)$_2$-20** were examined for conversion to the corresponding chlorin. Given (1) the difficulty of separation of the *Z* and *E* isomers, (2) the dominance of the *Z* isomer in **20** (8.5:1) and presumed *Z* in **19** (6:1 ratio by ^{1}H NMR spectroscopy) and **21** (6:1), and (3) the expectation that the *Z* (but not the *E*) isomer would be a suitable substrate for the Nazarov reaction, we used the mixture of *Z*/*E* isomers for the subsequent ring-closure reactions (Scheme 5). Survey reactions of **19** or **20** at small scale were monitored by absorption spectroscopy, and the yield was calculated on the basis of a molar absorption coefficient at the Q_y band [assuming[39] ε_{Q_y} (647 nm) = 34,700 M^{-1} cm^{-1}]. The reaction under the conditions employed for formation of the bacteriochlorophyll skeleton ($Yb(OTf)_3$ in refluxing CH_3CN)[19] did not afford the chlorin product. The next-best catalysts for the bacteriochlorophyll skeleton reaction were $Sc(OTf)_3$ and $In(OTf)_3$. The use of $Sc(OTf)_3$ in some cases gave a peak characteristic of a small amount of bacteriochlorin (<10%), which may originate from a retro-Knoevenagel reaction followed by self-condensation of the liberated AD half. We explored ∼14 Lewis acids, several additives (2,6-di-*tert*-butylpyridine, DDQ, *p*-chloranil, and $LiClO_4$), various solvents (MeCN, CH_2Cl_2, DCE, and toluene) over increasing temperatures (rt, 40, 65, 80, and 100 °C), and a range of concentrations (0.1, 0.2, 3, and 5 mM) of **19** and **20** (see the Supporting Information). The conditions for bacteriochlorin formation (without the isocyclic ring), which entail catalysis by TMSOTf in the presence of 2,6-di-*tert*-butylpyridine,[31] also were examined. Ultimately, we found that the best conditions here included both $In(OTf)_3$ and $InCl_3$ in refluxing CH_3CN for 20 h.

Scheme 5. One-Flask Formation of the Chlorophyll Skeleton



Application of such conditions to enones **19** and **20** gave the corresponding chlorin as the indium chelate **22** in ∼8% yield and **23** in 16% yield (assessed by absorption spectroscopy) and in isolated yields of ∼5 and 13%, respectively (Scheme 5). The xylyl-substituted enone **21** gave the corresponding indium chlorin **24** in 49% yield. Similar disparities in yields have been observed in the synthesis of chlorins without versus with meso-substituents.[2] Application of the conditions to **(Boc)$_2$-19** and **(Boc)$_2$-20** did not afford the corresponding chlorin. Attempts to remove the Boc groups by treatment with TFA or TMSI did not give either the deprotected dipyrromethane or the chlorin product (see the Supporting Information).

Analysis of indium chlorins **22**−**24** was carried out by matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS) with the matrix *α*-cyano-4-hydroxycinnamic acid (4-CHCA) and by electrospray ionization mass spectrometry (ESI−MS). MALDI-MS analysis in the positive-ion mode of tetrapyrroles is known to afford ionized analytes wherein electron loss (i.e., formation of the tetrapyrrole cation radical, M^+) can be accompanied by the more typical protonation ($M + H^+$).[40] The molecular ion of the indium chelate containing a chloride counterion was observed for **23** (MALDI-MS) and for **24** (ESI−MS); loss of the counterion was observed for **22** and **23** (ESI−MS) and **24** (MALDI-MS); and **22** gave no signal by MALDI-MS. Thus, the nature of the apical counterion remains unestablished for **22** but is assumed to be chloride.

The absorption spectra of indium chlorins **22**−**24** are shown in Figure 3. The indium chlorins exhibit a strong long-wavelength (Q_y) absorption band (647, 651, 651 nm) in the red region along with a strong absorption band in the near-ultraviolet and blue regions (419, 423, 429 nm). The spectra closely mirror that of the magnesium-containing chlorophyll *a*,[41] which exhibits peak maxima at 430 and 662 nm in CH_3CN. The absorption spectrum of chlorophyll *a* is rather

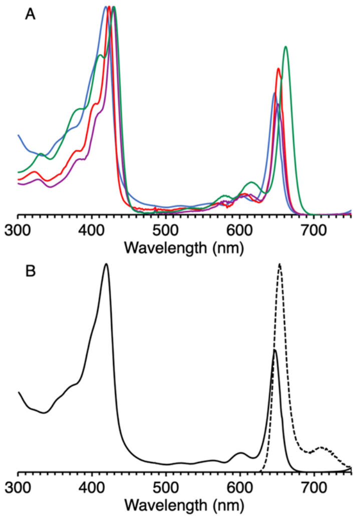
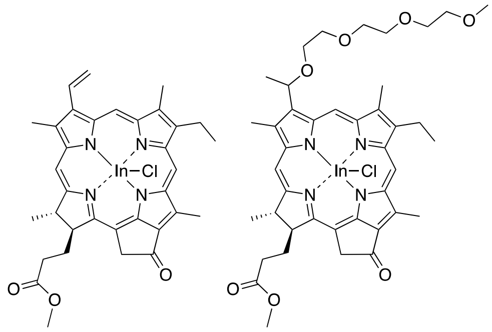


Figure 3. Panel A: Absorption spectra of **22** (blue line), **23** (red line), **24** (purple line), and chlorophyll *a* (green line) in CH_3CN at room temperature (normalized in the Soret band). The peak absorption in the red region is at ~647 nm (**22**), 652 nm (**23**), 651 nm (**24**), and 662 nm (chlorophyll *a*). Panel B: Absorption spectrum (solid line) and fluorescence spectrum (dashed line, 654 nm, Stokes shift = 7 nm) of **22** in CH_3CN at room temperature.

insensitive to solvent, with <3 nm difference in the positions of the peak maxima in CH_3CN (here) and the well-known spectrum in diethyl ether.[42] The spectra of indium chlorins **22**−**24** also are nearly identical to those of the few reported[43−46] indium chelates of ligands derived from chlorophyll *a*, of which the two shown in Chart 2 are representative (unspecified solvents): (1) **MV6401**,[44] a methyl pyropheophorbide derivative, which exhibits absorption[43] at 423 nm (ε = 101,000 M^{-1} cm^{-1}) and 659 nm (74,000 M^{-1} cm^{-1}) and has been examined for photodynamic therapy; and (2) **In-PP-9**, which lacks the 3-vinyl group and exhibits the Q_y band at 651 nm.[44]

Chart 2. Representative ClIn(III) Chelates of Chlorophyll-Derived Ligands.



MV-6401 **In-PP-9**

The fluorescence properties of the indium chlorins **22**−**24** were measured in CH_3CN at room temperature. Illumination in the Soret region (430 nm) resulted in emission in the red region, with Stokes shift of 7, 3, and 6 nm, for **22**−**24**, respectively. A representative fluorescence emission spectrum is shown in Figure 3, panel B (all spectra are shown in the Supporting Information). The fluorescence quantum yield (Φ_f) values were determined using chlorophyll *a* (in diethyl ether) as a standard, which exhibits Φ_f = 0.32. The values were 0.09 for **22**−**24**. To our knowledge, Φ_f values have not been reported previously for indium chlorins.

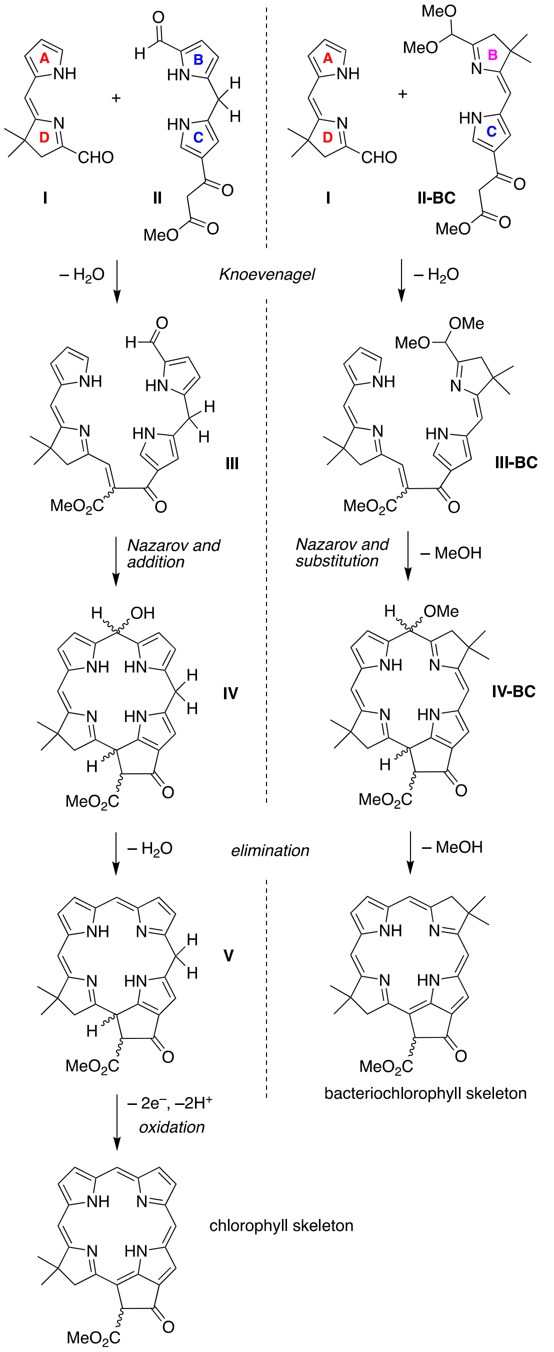
Each indium chlorin **22**−**24** is expected to exist as a mixture of diastereomers due to the presence of a stereocenter at the 13^2-position and the apical indium(III) chloride. The ^1H NMR spectrum of each of **22**−**24** indeed showed the presence of two sets of peaks characteristic of magnetically inequivalent environments for the following protons (data for **22**): the proton at the 13^2-position (singlets, δ 5.96 and 6.31 ppm), the pyrroline CH_2 at the 17-position (AB pattern, δ 4.10−4.42 ppm), and the two methyl groups at the 18-position (singlets, δ 1.95 and 2.08 ppm). The diastereomeric mixture could not be separated by silica gel chromatography. In this regard, the β-ketoester motif embedded in the isocyclic ring is well known to undergo epimerization even in neutral solution owing to exchange of the central proton,[47,48] which complicates separation schemes.

4. Comparison of Reactions and Reactivity. The challenges associated with identifying reaction conditions for the conversion of enones **19**−**21** to chlorophyll skeletons **22**−**24** were surprising, especially given the facile analogous synthesis[19] of the bacteriochlorophyll skeleton (Scheme 2). The two processes are compared in a formal manner in Scheme 6, with the exception of the indium chelation process, the role of which is unclear because indium(III) chelation could occur with several intermediates on the path to the indium chlorin. Knoevenagel condensation appears identical in the two processes, affording **III** or **III-BC**. The macrocyclization via carbon−carbon bond formation proceeds via addition or substitution to give the carbinol **IV** or the methoxy derivative **IV-BC**, respectively, where the macrocyclization is accompanied or preceded by Nazarov reaction. The path toward aromatization entails elimination of one molecule of water from **IV** to form the dihydrochlorophyll **V** followed by $2e^-/2H^+$ dehydrogenation to give the final chlorophyll skeleton, whereas elimination of one molecule of methanol converts **IV-BC** directly to the bacteriochlorophyll skeleton. The order of events in the series leading from **III** or **III-BC** is not known, but comparison highlights the importance of an oxidant for the overall transformation yielding the chlorophyll skeleton. An oxidant would not be required if the dipyrromethane BC half **II** were replaced with a dipyrrin, but our attempts to do so have not yet been successful. Note that both halves in the formation of the bacteriochlorin are dihydrodipyrrins (i.e., fully unsaturated except for the necessary saturation to give the pyrroline ring), whereupon an oxidant is not required.

A striking feature of the Knoevenagel reaction[49−51] of **I** (**17**, **18**) and **II** (**2**, $(\mathbf{Boc})_2$-**2**, **15**) is the presence of four carbonyl groups. Three pyrroles are also present that can potentially compete with the active methylene group for reaction with a carbonyl group. Hence, the question arises as to why cross-reaction does not significantly interfere with the successful formation of **III**.

The most reactive carbonyl in the two-halves is the aldehyde in ring D, whereas that in ring B is a "vinylogous amide".[52] The remaining two carbonyls are a vinylogous ketone (ring C) and an ester. The relative unreactivity of pyrrole−carboxaldehydes has been textbook knowledge since at least 1960,[53] was encountered by Woodward in his chlorophyll campaign,[54] and originates from resonance delocalization with the pyrrole nitrogen.[55] Quantitative reactivity scales for aldehydes as electrophiles do not include either the pyrroline-2-carbox-

Scheme 6. Processes Leading to the Chlorophyll and Bacteriochlorophyll Skeleton



aldehyde (ring D) or the pyrrole-2-carboxaldehyde (ring B),[56,57] but toward opposite ends of one scale are respective analogues ethyl glyoxalate and 4-(dimethylamino)-benzaldehyde.[57] These two extremes would seem to correspond to the aldehydes of the dihydrodipyrrin and the pyrrole, respectively (Figure 4).

The nucleophilicity of pyrrole is very sensitive to the presence of electron-withdrawing or electron-releasing substituents.[58,59] Each of the three pyrroles in **I** and **II** bears one deactivating group—ring A is part of a dihydrodipyrrin–carboxaldehyde, and rings B and C each contain a carbonyl substituent. The Knoevenagel reaction (of **I** and **II** to form **III**) takes place under mild conditions at near-neutral pH wherein the active methylene is apparently more reactive than any of the pyrroles. The subsequent Nazarov cyclization and electrophilic aromatic substitution proceed in the presence of trivalent lanthanide catalysts under more forcing conditions (80 °C). Nazarov reactions find increasing use in heterocyclic chemistry[60−62] but have been employed infrequently with pyrroles bearing a propenoyl group at the 3-position.[19,63−65] The intramolecular juxtaposition of the carboxaldehyde of ring B and the pyrrolic unit of ring A in **III** likely facilitates the reaction of these intrinsically lesser reactive species in the electrophilic substitution giving rise to **IV**. Further studies are required to probe the sequence of events leading from **III** to **V**, to explore milder conditions for the Nazarov and accompanying reactions (including substitutes for InX$_3$), and ultimately to assess whether this general approach can accommodate the array of substituents present in native chlorophylls. Broad access in this regard would provide a valuable complement to the existing methods of semisynthesis[47,66−68] that begin with chlorophyll *a*.

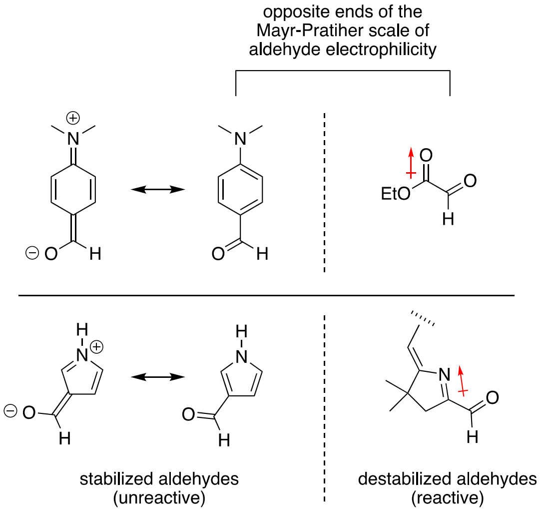


Figure 4. Comparison of aldehyde reactivity.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR and ^{13}C NMR spectra were collected at room temperature unless noted otherwise. Absorption spectra were collected in CH$_3$CN at room temperature. Molecular sieves (3 Å, powder) were heated (>100 °C) overnight prior to use. CHCl$_3$ contained amylenes as a stabilizer. THF used in all reactions was freshly distilled from Na/benzophenone ketyl unless noted. Silica gel (40 μm average particle size) was used for column chromatography. The column chromatography conditions are generally stated in the following format: [adsorbent, R_f with a TLC solvent, TLC visualization method, column chromatography eluent]. All commercially available compounds were used as received. Noncommercial compound **3a** was prepared as described in the literature.[29] Compounds **1**,[26] **4**,[28] **17**,[19] and **18**[19] were previously prepared in our group.

2-Bromo-10,11-bis(*N*-*tert*-butoxycarbonyl)-9-formyldipyrromethane ((Boc)$_2$-1). Following a reported procedure,[27] a solution of **1** (460. mg, 1.83 mmol) and 4-(dimethylamino)pyridine (45 mg, 0.37 mmol) in acetonitrile (7.5 mL) was treated with di-*tert*-butyl dicarbonate (1.60 g, 7.32 mmol) at room temperature. The mixture was stirred for 16 h at room temperature. The reaction mixture was concentrated, and the residue was purified by chromatography [silica, R_f = 0.70 in hexanes/ethyl acetate (5:1), visualized by phosphomolybdic acid stain, hexanes/ethyl acetate (5:1)] to afford a viscous yellow oil (780 mg, 95%): ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.51 (s, 9H), 1.54 (s, 9H), 4.39 (s, 2H), 5.81 (d, *J* = 2.1 Hz, 1H), 5.93 (d, *J* = 0.8 Hz, 1H), 7.05 (d, *J* = 3.8 Hz, 1H), 7.25 (d, *J* = 1.0 Hz, 1H), 9.99 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 27.6, 27.8, 29.0, 84.6, 85.9, 99.3, 112.6, 115.3, 120.6, 121.2, 132.5, 135.1, 140.0, 148.1, 148.9, 180.7; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{25}BrN_2O_5Na$ 475.0839, found 475.0831.

10,11-Bis(*N*-*tert*-butoxycarbonyl)-2-(3-methoxy-3-oxopropanoyl)-9-formyldipyrromethane ((Boc)$_2$-2). Following a reported procedure,[19] a mixture of **(Boc)$_2$-1** (200. mg, 0.442 mmol), methyl potassium malonate (103 mg, 0.659 mmol), Xantphos (127 mg, 0.219 mmol), $MgCl_2$ (63 mg, 0.66 mmol), and imidazole (60. mg, 0.88 mmol) was placed in a 25 mL Schlenk flask, which was charged with argon. THF (10.0 mL) was added followed by Et_3N (92 μL, 0.67 mmol). The mixture was degassed by three freeze−pump−thaw cycles. Then, $Pd(OAc)_2$ (49 mg, 0.22 mmol) and $Co_2(CO)_8$ (75 mg, 0.22 mmol) were added under a stream of argon. The flask was sealed immediately and heated at 65 °C in an oil bath, with reaction progress monitored by TLC. When the reaction was complete (48 h), the reaction mixture was allowed to cool to room temperature. The mixture was diluted with ethyl acetate and then filtered through a Celite pad. The filtrate was washed with brine and water, dried (Na_2SO_4), concentrated, and purified by chromatography [silica, R_f = 0.50 in hexanes/ethyl acetate (3:1), hexanes/ethyl acetate (3:1)] to afford a pale yellow oil (120 mg, 57%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 3H), 1.55 (s, 3H), 3.74 (s, 3H), 3.76 (s, 2H), 4.40 (s, 2H), 5.88 (d, *J* = 3.8 Hz, 1H), 6.28 (d, *J* = 1.5 Hz, 1H), 7.04 (d, *J* = 3.8 Hz, 1H), 7.90 (dd, *J* = 2.0, 0.7 Hz, 1H), 9.98 (s, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 27.6, 27.7, 29.0, 46.3, 52.4, 85.8, 85.9, 111.5, 112.4, 121.2, 125.1, 126.7, 133.4, 135.0, 139.9, 148.2, 148.8, 167.7, 180.7, 186.9; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{30}N_2O_8Na$ 497.1894, found 497.1890.

1-Formyl-8-(3-methoxy-3-oxopropanoyl)dipyrromethane (2). **From 7**: Following a reported procedure,[31] in one flask, a solution of **7** (434 mg, 1.17 mmol) in distilled THF (30 mL) and dry methanol (3 mL) under argon was treated with NaOMe (346 mg, 5.86 mmol), and the mixture was stirred for 45 min at room temperature. In a second flask, a solution of NH_4OAc (36 g) in water (60 mL) was bubbled with argon for 15 min prior to the addition of a solution of $TiCl_3$ (20% w/v in 2 N HCl solution, 7.2 mL). The mixture was stirred for another 15 min. Then the mixture in the first flask was transferred via cannula to the buffered $TiCl_3$ solution in the second flask. The resulting mixture was stirred at room temperature under argon for 20 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The organic extract was washed (brine/water), dried (Na_2SO_4), concentrated, and purified by chromatography [silica, hexanes/ethyl acetate (1:2)] to give a white solid (130 mg, 40%): mp 131−133 °C; ^{1}H NMR (300 MHz, THF-d_8) δ 3.60 (s, 3H), 3.67 (s, 2H), 3.95 (s, 2H), 5.96−6.01 (m, 1H), 6.31−6.36 (m, 1H), 6.78−6.82 (m, 1H), 7.36−7.40 (m, 1H), 9.37 (s, 1H), 10.52 (br, 1H), 11.24 (br, 1H); ^{13}C{^{1}H} NMR (75 MHz, THF-d_8) δ 25.8, 45.7, 50.8, 106.5, 109.1, 120.4, 123.9, 125.3, 130.3, 132.9, 138.1, 167.9, 177.3, 185.5; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{14}H_{15}N_2O_4$, 275.1026, found 275.1023. **From (Boc)$_2$-2:** A solution of **(Boc)$_2$-2** (35 mg, 0.074 mmol) in CH_2Cl_2 (10 mL) was treated with TFA (2.5 mL) and stirred at room temperature under air. The reaction was monitored by TLC. After 1.5 h, if there was no desired product formation, another aliquot of TFA (2.5 mL) was added, and the reaction was allowed to continue for 1 h. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated to a crude yellow solid. Purification by chromatography on a short column [silica, R_f = 0.11 in hexanes/ethyl acetate (1:1), hexanes/ethyl acetate (1:1 to 1:3)] afforded a pale yellow solid (14 mg, 69%). The product gave ^{1}H NMR, ^{13}C NMR and HRMS data identical with that above.

6-(4-Bromo-1-tosylpyrrol-2-yl)-1,1-dimethoxy-5-nitrohexan-2-one (5). Following a reported procedure[28] with modification, a solution of **4** (5.62 g, 15.1 mmol) and **3** (2.16 g, 16.6 mmol) in distilled THF (150 mL) at −78 °C under argon was treated dropwise with DBU (3.45 g, 22.7 mmol). After 10 min, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed thoroughly with brine and water, dried (Na_2SO_4), concentrated, and purified by chromatography [silica, hexanes/ethyl acetate (3:1)] to give a brown oil (5.5 g, 72%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08−2.15 (m, 2H), 2.39 (s, 3H), 2.62 (t, *J* = 7.2 Hz, 2H), 3.12 (ABX, $\Delta\delta_{AB}$ = 0.14, *J* = 15.8 Hz, 1H), 3.21 (ABX, $\Delta\delta_{AB}$ = 0.17, *J* = 15.8 Hz, 1H), 3.37 (d, *J* = 0.6 Hz, 6H), 4.43 (s, 1H), 4.69−4.89 (m, 1H), 6.03 (d, *J* = 1.7 Hz, 1H), 7.26 (d, *J* = 1.8 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 21.7, 26.8, 31.4, 33.0, 54.9, 86.9, 100.7, 103.9, 117.5, 122.3, 126.7, 129.2, 130.4, 135.2, 145.9, 203.5; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{24}BrN_2O_7S$ 503.0482, found 503.0483.

6-[4-(3-Methoxy-3-oxopropanoyl)-1-tosylpyrrol-2-yl]-1,1-dimethoxy-5-nitrohexan-2-one (6). Following a reported procedure,[19] a mixture of **5** (5.60 g, 11.2 mmol), methyl potassium malonate (2.61 g, 17.0 mmol), Xantphos (3.23 g, 5.80 mmol), $MgCl_2$ (1.59 g, 17.0 mmol), and imidazole (1.47 g, 22.3 mmol) was placed in a 250 mL Schlenk flask, which was charged with argon. THF (110 mL) was added followed by Et_3N (2.32 mL, 17.0 mmol). The mixture was degassed by three freeze−pump−thaw cycles. Then, $Pd(OAc)_2$ (1.25 g, 5.80 mmol) and $Co_2(CO)_8$ (1.92 g, 5.80 mmol) were added under a stream of argon. The flask was sealed immediately and heated at 65 °C in an oil bath for 48 h, with reaction progress monitored by TLC. After 48 h, TLC analysis showed remaining starting material; thus, $Pd(OAc)_2$ (0.63 g, 2.9 mmol) and $Co_2(CO)_8$ (0.96 g, 2.9 mmol) were added under a stream of argon, and the reaction was continued for 24 h. The reaction mixture was diluted with ethyl acetate and filtered through a Celite pad. The filtrate was washed with brine and water, dried (Na_2SO_4), concentrated, and purified by chromatography [silica, CH_2Cl_2/ethyl acetate (10:1)] to give a light-yellow oil (3.30 g, 56%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05−2.12 (m, 2H), 2.38 (s, 3H), 2.59 (t, *J* = 7.1 Hz, 2H), 3.17 (ABX, $\Delta\delta_{AB}$ = 0.19, *J* = 15.9 Hz, 1H), 3.19 (ABX, $\Delta\delta_{AB}$ = 0.21, *J* = 16.0 Hz, 1H), 3.34 (d, *J* = 0.6 Hz, 6H), 3.65 (s, 3H), 3.71 (s, 2H), 4.40 (s, 1H), 4.65−4.86 (m, 1H), 6.40 (d, *J* = 1.6 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.90 (d, *J* = 1.8 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 21.6, 26.8, 31.2, 32.9, 46.4, 52.4, 54.9, 86.5, 103.9, 113.1, 126.0, 127.0, 128.0, 130.0, 130.6, 134.5, 146.5, 167.4, 186.4, 203.5; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{29}N_2O_{10}S$ 525.1537, found 525.1534.

6-[4-(3-Methoxy-3-oxopropanoyl)pyrrol-2-yl]-1,1-dimethoxy-5-nitrohexan-2-one (7). Following a reported procedure,[19] a sample of **6** (2.85 g, 5.44 mmol) was treated with TBAF (1.0 M in THF, 5.5 mL, 5.5 mmol) in a 20 mL flask and heated to 65 °C in an oil bath for 1 h. The mixture was allowed to cool to room temperature, quenched by the addition of saturated aqueous $NaHCO_3$ solution, and then extracted with ethyl acetate. The organic extract was washed (brine and water), dried (Na_2SO_4), concentrated, and purified by chromatography [silica, hexanes/ethyl acetate (1:2)] to give a light-yellow solid (1.44 g, 71%): mp 56−58 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99−2.15 (m, 2H), 2.59 (t, *J* = 7.1 Hz, 2H), 3.11 (ABX, $\Delta\delta_{AB}$ = 0.16, *J* = 15.5 Hz, 1H), 3.14 (ABX, $\Delta\delta_{AB}$ = 0.17, *J* = 15.5 Hz, 1H), 3.31 (s, 6H), 3.63 (s, 3H), 3.73 (s, 2H), 4.42 (s, 1H), 4.62−4.85 (m, 1H), 6.31−6.35 (m, 1H), 7.30−7.47 (m, 1H), 10.07 (br, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 26.4, 31.5, 33.2, 46.1, 52.3, 54.8, 87.0, 103.6, 107.7, 124.9, 125.5, 128.3, 168.7, 187.8, 204.2; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{23}N_2O_8$ 371.1449, found 371.1446.

2-(3,5-Dimethylbenzoyl)pyrrole (8). Following a reported procedure,[26] a solution of ethylmagnesium bromide (53 mL, 0.16 mol, 3 M in diethyl ether) flushed with argon was slowly treated with freshly distilled pyrrole (10.0 mL, 9.67 g, 0.145 mol) in anhydrous diethyl ether (150 mL), which caused a slight reflux. The mixture continued to reflux for 30 min, and then was allowed to cool to room temperature. A solution of 3,5-dimethylbenzoyl chloride (29.3 g, 0.174 mol) in diethyl ether (100 mL) was added dropwise over 2 h under argon, where the color changed from brown to dark-red. The mixture was stirred for 15 h at room temperature, and then was treated with saturated aqueous ammonium chloride (100 mL). The resulting precipitate was dissolved in CH_2Cl_2, and the organic layer was washed with water, dried (Na_2SO_4), and concentrated to a dark-red solid. The crude solid was purified by chromatography [silica, R_f = 0.35 in CH_2Cl_2, CH_2Cl_2 to CH_2Cl_2/ethyl acetate (3:1)] to afford a pale yellow solid (18.1 g, 62%): mp 136−139 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.39 (s, 6H), 6.33 (dt, J_1 = 3.8 Hz, J_2 = 2.5 Hz, 1H), 6.88−6.90 (m, 1H), 7.14 (q, J = 1.4 Hz, 1H), 7.19−7.21 (m, 1H), 7.48−7.52 (m, 2H), 9.79 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.3, 110.9, 119.4, 125.1, 126.7, 131.3, 133.5, 138.0, 138.4, 185.3; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_{14}NO$ 200.1070, found 200.1066.

4-Bromo-2-(3,5-dimethylphenyl)pyrrole (9-Br). A stirred solution of **8** (5.0 g, 0.025 mol) in THF (ACS grade, 100 mL) under argon at 0 °C was treated portionwise with *N*-bromosuccinimide (4.7 g, 0.026 mol). The reaction progress was monitored by TLC. After 40 min, all the starting material was consumed, and the mixture was allowed to warm to room temperature. The solvent was removed via rotary evaporation. The resulting pale-yellow solid was dissolved in ethyl acetate and washed with water, dried (Na_2SO_4), and concentrated to a white solid. The crude solid was purified by chromatography [silica, R_f = 0.72 in hexanes/ethyl acetate (3:1), hexanes/ethyl acetate (6:1 to 2:1)] to afford a white solid (4.8 g, 70%): mp 174−178 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.40 (s, 6H), 6.87 (dd, J_1 = 2.7 Hz, J_2 = 1.4 Hz, 1H), 7.10 (dd, J_1 = 3.0 Hz, J_2 = 1.4 Hz, 1H), 7.22 (d, J = 2.0 Hz, 1H), 7.46−7.49 (m, 2H), 9.52 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.3, 98.2, 120.5, 124.9, 126.7, 131.1, 134.1, 137.7, 138.2, 184.8; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_{13}BrNO$ 278.0175, found 278.0177.

4-Iodo-2-(3,5-dimethylphenyl)pyrrole (9-I). A stirred solution of **8** (3.84 g, 19.3 mmol) in anhydrous DMF (96 mL) was treated with NIS (4.33 g, 19.3 mmol) in one batch at 0 °C under argon. Then the reaction mixture was allowed to warm to room temperature over 30 min followed by heating at 70 °C in an oil bath for 35 h. Then the reaction mixture was allowed to cool to room temperature over 30 min and quenched by the addition of 20% $Na_2S_2O_3$ aqueous solution. The organic layer was separated, dried (Na_2SO_4), and concentrated to a brown solid, which then was purified by chromatography [silica, hexanes/ethyl acetate (10:1)]. The starting material **8** was recovered (2.60 g, 67%). The title product was obtained as a yellow solid (1.73 g, 27%): mp 169−170 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.40 (s, 6H), 6.94−6.98 (m, 1H), 7.17 (d, J = 2.9 Hz, 1H), 7.22 (s, 1H), 7.47 (s, 2H), 9.91 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.3, 62.3, 125.2, 126.7, 129.6, 132.7, 134.0, 137.7, 138.2, 184.4; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_{13}INO$ 326.0036, found 326.0032.

2-Bromo-5-(3,5-dimethylphenyl)dipyrromethane (10). Following a reported procedure[26] with modification, a solution of **9-Br** (3.40 g, 12.2 mmol) in anhydrous THF/methanol (180 mL, 8:1, v/v) at 0 °C was treated with $NaBH_4$ (7.38 g, 195 mmol) under argon. The mixture was stirred for 2 h. Then water was added, and the resulting mixture was extracted with ethyl acetate. The organic layer was separated, dried (Na_2SO_4), and concentrated to a pale-yellow oil. The resulting mixture was dissolved in anhydrous acetonitrile (16 mL), whereupon freshly distilled pyrrole (19.4 mL) was added. The solution was degassed with a stream of argon for 5 min and then treated with $InCl_3$ (329 mg, 1.49 mmol). The mixture was stirred for 15 h under argon at room temperature and then treated with 5.0 M NaOH (30 mL). After extraction with ethyl acetate, the organic layer was dried (Na_2SO_4) and concentrated. The dark oil was washed with hexanes, sonicated, and concentrated. The excess pyrrole could be recovered by rotary evaporation. The resulting dark-brown oil was purified by chromatography [silica, R_f = 0.37 in hexanes/CH_2Cl_2/ethyl acetate (30:10:3), visualized in an iodine chamber, hexanes/CH_2Cl_2/ethyl acetate (10:1:1 to 30:10:3), 5% Et_3N] to afford a yellow oil that turned dark-brown upon storage (3.18 g, 79%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.26 (s, 6H), 5.26 (s, 1H), 5.88−5.90 (m, 1H), 5.91 (dd, J_1 = 3.4 Hz, J_2 = 2.3 Hz, 1H), 6.13 (q, J = 2.9 Hz, 1H), 6.58 (t, J = 2.2 Hz, 1H), 6.63 (q, J = 2.3 Hz, 1H), 6.78 (d, J = 1.8 Hz, 2H), 6.89 (s, 1H), 7.80 (br s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.4, 43.9, 96.2, 107.4, 108.5, 109.8, 116.9, 117.5, 126.2, 129.0, 131.8, 133.7, 138.5, 141.1; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{17}H_{16}BrN_2$ 327.0523, found 327.0496.

5-(3,5-Dimethylphenyl)dipyrromethane (11). Reaction of **9-I** (451 mg, 1.39 mmol), $NaBH_4$ (839 mg, 22.2 mmol), pyrrole (2.2 mL), and $InCl_3$ (37.4 mg, 0.169 mmol) under the general procedure described for **10** followed by chromatography [silica, hexanes/ethyl acetate (10:1)] gave a brown oil (232 mg, 66%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.27 (s, 6H), 5.40 (s, 1H), 5.93 (d, J = 3.7 Hz, 2H), 6.16 (q, J = 2.9 Hz, 2H), 6.69 (q, J = 2.4 Hz, 2H), 6.84 (s, 2H), 7.91 (br s, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 21.4, 43.9, 107.0, 108.4, 117.0, 126.2, 128.7, 132.6, 138.2, 141.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{19}N_2$ 251.1543, found 251.1538.

8-Bromo-5-(3,5-dimethylphenyl)-1-formyldipyrromethane (12). Following a reported procedure[26] with modification, a sample of anhydrous DMF (21 mL) was treated with $POCl_3$ (3.00 mL, 32.7 mmol) at 0 °C under argon, and the mixture was stirred for 8 min. Then a solution of **10** (3.18 g, 9.66 mmol) in anhydrous DMF (26.0 mL) was treated with the freshly prepared Vilsmeier reagent (6.38 mL) under argon at 0 °C. The resulting mixture was stirred for 2.5 h, and the reaction progress was monitored by TLC. The reaction was quenched by the addition of saturated aqueous sodium acetate (100 mL) and then stirred for 40 min at 0 °C. The mixture was extracted with CH_2Cl_2 (100 mL). The organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated to a dark-brown oil. The residue was purified by chromatography [silica, R_f = 0.36 in hexanes/ethyl acetate (3:1), visualized by 2,4-dinitrophenylhydrazine stain, hexanes/ethyl acetate (3:1 to 1:1)] to give a yellow oil, which turned to a solid upon storage at −20 °C (2.34 g, 68%): mp 127−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 6H), 5.38 (s, 1H), 5.97 (t, J = 1.9 Hz, 1H), 6.12 (dd, J_1 = 3.9 Hz, J_2 = 2.5 Hz, 1H), 6.69 (t, J = 2.2 Hz, 1H), 6.74 (d, J = 1.6 Hz, 2H), 6.89 (dd, J_1 = 3.9 Hz, J_2 = 2.5 Hz, 1H), 6.91 (s, 1H), 8.24 (br s, 1H), 9.23 (s, 1H), 9.56 (br s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.3, 44.0, 96.4, 110.4, 110.9, 117.6, 122.1, 126.0, 129.5, 131.6, 132.4, 138.8, 139.2, 141.6, 178.7; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{18}H_{18}BrN_2O$ 357.0597, found 357.0598.

8-Bromo-10,11-bis(*N-tert*-butoxycarbonyl)-5-(3,5-dimethylphenyl)-1-formyldipyrromethane ((Boc)$_2$-12). A solution of **12** (2.16 g, 6.05 mmol) and 4-(dimethylamino)pyridine (148 mg, 1.21 mmol) in acetonitrile (130 mL) was treated with di-*tert*-butyl dicarbonate (6.60 g, 30.3 mmol) at room temperature. The mixture was stirred for 16 h and then treated with additional di-*tert*-butyl dicarbonate (50. mg, 0.23 mmol). The resulting mixture was stirred for 1 h at room temperature. Removal of the solvent afforded an oil, which was purified by chromatography [silica, R_f = 0.67 in hexanes/ethyl acetate (5:1), visualized by phosphomolybdic acid stain, hexanes/ethyl acetate (5:1)] to afford a pale-yellow oil (2.59 g, 77%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.38 (s, 9H), 1.43 (s, 9H), 2.26 (s, 6H), 5.54 (dd, J = 2.1, 1.0 Hz, 1H), 5.67 (dd, J_1 = 3.8 Hz, J_2 = 0.8 Hz, 1H), 6.41 (s, 1H), 6.67 (d, J = 1.6 Hz, 2H), 6.87−6.89 (m, 1H), 6.97 (d, J = 3.8 Hz, 1H), 7.27 (d, J = 2.0 Hz, 1H), 9.80 (s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.3, 27.3, 27.7, 43.3, 84.8, 85.6, 99.0, 112.7, 116.9, 121.2, 121.2, 126.8, 128.8, 134.6, 136.4, 137.8, 139.5, 144.3, 147.9, 148.8, 180.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{28}H_{34}BrN_2O_5$ 557.1646, found 557.1640.

8-Bromo-5-(3,5-dimethylphenyl)-1-formyldipyrrin (13). A solution of **12** (36 mg, 0.10 mmol) in THF (ACS grade, 3.0 mL) was treated portionwise with a solution of DDQ (23 mg, 0.10 mmol) in THF (ACS grade, 3.0 mL) whereupon the color changed from yellow to dark-brown. The reaction mixture was stirred at room temperature under air. The reaction process was monitored by TLC. After 50 min, the mixture was poured into a 100 mL beaker containing water (20 mL) and $CHCl_3$ (30 mL). The resulting mixture was stirred for 10 min, and then the organic layer was separated, dried (Na_2SO_4), and concentrated to a dark-yellow oil. The residue was purified by chromatography [silica, the product spot tailed in $CHCl_3$/methanol (100:1), R_f = 0.09−0.54, $CHCl_3$/methanol (100:1)] to afford a red-orange oil (20 mg, 56%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 6H), 6.40 (d, J = 4.1 Hz, 1H), 6.88 (d, J = 4.1 Hz, 1H), 6.90 (d, J = 1.0 Hz, 1H), 7.04 (d, J = 0.8 Hz, 2H), 7.17−7.12 (m, 1H), 9.70 (s, 1H), 12.77 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.3, 116.4, 119.6, 121.8, 128.3, 131.2, 134.4, 135.7, 137.6, 137.7, 137.7, 140.5, 150.9, 160.9, 180.3; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{18}H_{16}BrN_2O$ 355.0441, found 355.0443.

8-Bromo-5-(3,5-dimethylphenyl)-1-(1,1-dimethoxymethyl)-dipyrrin (14). Following a reported procedure,[37] a solution of **13** (20. mg, 0.056 mmol) in trimethyl orthoformate (2.5 mL) was treated with TsOH·H_2O (32 mg, 0.17 mmol). The reaction mixture was stirred at room temperature for 1 h. Then, the mixture was diluted with ethyl acetate, and the resulting solution was slowly poured into a beaker containing saturated aqueous $NaHCO_3$. The organic layer was separated, washed with water, dried (Na_2SO_4), and concentrated to a dark-red oil. The residue was purified by chromatography [silica, R_f = 0.80 in hexanes/ethyl acetate (3:1), hexanes/ethyl acetate (3:1)] to afford a red-orange oil (13 mg, 62%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 6H), 3.41 (s, 6H), 5.55 (s, 1H), 6.33 (d, *J* = 4.1 Hz, 1H), 6.49 (d, *J* = 4.1 Hz, 1H), 6.72 (d, *J* = 1.1 Hz, 1H), 7.06 (s, 2H), 7.11 (s, 1H), 7.65 (d, *J* = 1.1 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.3, 52.8, 98.7, 109.5, 112.9, 126.6, 128.46, 130.8, 131.3, 135.9, 136.5, 137.2, 142.6, 144.5, 146.4, 151.0; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{20}H_{22}BrN_2O_2$ 401.0859, found 401.0857.

10,11-Bis(*N-tert*-butoxycarbonyl)-2-(3-methoxy-3-oxopropanoyl)-5-(3,5-dimethylphenyl)-9-formyldipyrromethane ((Boc)$_2$-15). Following a reported procedure,[19] a mixture of **(Boc)$_2$-12** (55 mg, 0.10 mmol), methyl potassium malonate (24 mg, 0.15 mmol), Xantphos (30. mg, 52 μmol), $MgCl_2$ (14.5 mg, 0.152 mmol), and imidazole (14 mg, 0.21 mmol) was placed in a 25 mL Schlenk flask, which was charged with argon. THF (10.0 mL) was added followed by Et_3N (208 μL, 1.51 mmol). The mixture was degassed by three freeze−pump−thaw cycles. Then, $Pd(OAc)_2$ (18 mg, 0.080 mmol) and $Co_2(CO)_8$ (27 mg, 0.079 mmol) were added under a stream of argon. The flask was sealed immediately and heated at 65 °C in an oil bath, with reaction progress monitored by TLC. When the reaction was complete (48 h), the reaction mixture was allowed to cool to room temperature. The mixture was diluted with ethyl acetate and then filtered through a Celite pad. The filtrate was washed with brine and water, dried (Na_2SO_4), concentrated, and purified by chromatography [silica, R_f = 0.60 in hexanes/ethyl acetate (2:1), visualized by phosphomolybdic acid stain, hexanes/ethyl acetate (1:1)] to afford a colorless oil that turned dark-yellow upon storage (41 mg, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 9H), 1.46 (s, 9H), 2.25 (s, 6H), 3.72 (s, 3H), 3.75 (s, 2H), 5.66 (d, *J* = 3.6 Hz, 1H), 6.00 (s, 1H), 6.39 (s, 1H), 6.66 (s, 2H), 6.89 (s, 1H), 6.97 (dd, *J* = 4.0, 1.7 Hz, 1H), 7.92 (s, 1H), 9.79 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.3, 27.3, 27.6, 43.2, 46.2, 52.4, 85.6, 86.0, 112.6, 113.0, 121.3, 124.8, 126.7, 127.5, 129.0, 134.6, 137.6, 137.9, 139.0, 144.0, 148.2, 148.7, 167.8, 179.9, 187.0; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{32}H_{38}N_2O_8Na$ 601.2520, found 601.2517.

9-Formyl-2-(3-methoxy-3-oxopropanoyl)-5-(3,5-dimethylphenyl)dipyrromethane (15). A solution of **(Boc)$_2$-15** (175 mg, 0.300 mmol) in CH_2Cl_2 (43 mL) was slowly treated with TFA (5.0 mL). The reaction process was monitored by TLC. Aliquots of TFA (5.0 mL, 5.0 mL, and 2.5 mL) were added after 30, 60, and 90 min, respectively. Then the mixture was stirred for 30 min at room temperature and slowly poured into a beaker containing 150 mL of saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4), and concentrated to a dark yellow oil. The resulting oil was purified by chromatography [silica, R_f = 0.21 in hexanes/ethyl acetate (1:1), visualized by phosphomolybdic acid stain, ethyl acetate] to afford a yellow oil (99 mg, 88%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.21 (s, 6H), 3.68 (s, 3H), 3.69 (s, 2H), 5.38 (s, 1H), 6.04−6.07 (m, 1H), 6.30 (dd, J_1 = 2.7 Hz, J_2 = 1.7 Hz, 1H), 6.71−6.73 (m, 2H), 6.84 (dd, J_1 = 3.9 Hz, J_2 = 2.4 Hz, 1H), 6.87−6.90 (m, 1H), 7.35 (dd, J_1 = 3.2 Hz, J_2 = 1.7 Hz, 1H), 9.08 (br s, 1H), 9.54 (s, 1H), 10.20 (br s, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 21.3, 43.6, 46.3, 52.4, 107.9, 111.3, 122.9, 124.9, 125.0, 126.0, 129.3, 132.5, 134.1, 138.5, 139.3, 142.6, 168.5, 178.9, 187.3; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{22}H_{23}N_2O_4$ 379.1652, found 379.1647.

2-Carbomethoxy-3-(2,3-dihydro-3,3-dimethyl-7-*p*-tolyldipyrrin-1-yl)-1-[1-formyldipyrromethan-8-yl]prop-2-ene-1-one (19). Following a reported procedure,[19] samples of **17** (72 mg, 0.25 mmol) and **2** (56 mg, 0.20 mmol) were dissolved in anhydrous CH_2Cl_2 (4.0 mL) containing dried molecular sieves 3 Å (60 mg, powder form) in a 50 mL flask under argon. A solution of piperidine/acetic acid in CH_2Cl_2 (1.3 mL, 60 mM/60 mM, 78 μmol/78 μmol) was added, and the mixture was stirred at room temperature for 20 h. The reaction process was monitored by TLC. The mixture was diluted with ethyl acetate (20 mL) and filtered through a Celite pad. The filtrate was concentrated to a dark-red gum and purified by chromatography [silica, hexanes/ethyl acetate (3:1 to 1:2)] to give a dark-red gum as a mixture of *Z*/*E* isomers [57 mg, 51%, R_f = 0.46, 0.44 in reversed-phase TLC, methanol/H_2O (5:1)]. The ^{1}H NMR spectrum showed a 6:1 ratio of the two isomers given by two resonances of the ring-B carboxaldehyde proton. A sample of 11 mg of the mixture was separated by reversed-phase TLC (methanol/H_2O, 10:1) followed by preparative TLC [silica, 1 mm thick, hexanes/ethyl acetate (5:4)] as a red gum (1.5 mg), affording the major isomer in pure form: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.05 (s, 6H), 2.38 (s, 3H), 2.52 (s, 2H), 3.80 (s, 3H), 4.01 (s, 2H), 6.12 (s, 1H), 6.15−6.18 (m, 1H), 6.26 (t, *J* = 2.7 Hz, 1H), 6.54 (s, 1H), 6.87 (t, *J* = 2.7 Hz, 1H), 6.94 (dd, J_1 = 3.9 Hz, J_2 = 2.4 Hz, 1H), 7.20 (d, *J* = 7.8 Hz, 2H), 7.24 (dd, J_1 = 3.2 Hz, J_2 = 1.7 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.62 (s, 1H), 9.21 (br s, 1H), 9.36 (s, 1H), 10.16 (br s, 1H), 10.64 (br s, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 21.1, 26.5, 28.9, 41.6, 50.5, 52.9, 107.2, 108.9, 109.4, 110.9, 120.9, 125.7, 126.3, 126.5, 127.3, 128.5, 129.2, 130.2, 132.5, 133.8, 134.9, 135.5, 137.5, 140.5, 160.8, 165.4, 167.0, 178.9, 188.3; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{33}H_{33}N_4O_4$ 549.2496, found 549.2493; λ_{abs} (CH_3CN) = 294 nm, 495 nm.

2-Carbomethoxy-3-(2,3-dihydro-3,3-dimethyl-7-*p*-tolyldipyrrin-1-yl)-1-[10,11-bis(*N-tert*-butoxycarbonyl)-1-formyldipyrromethan-8-yl]prop-2-ene-1-one ((Boc)$_2$-19). Following a reported procedure,[19] samples of **17** (30.0 mg, 103 μmol) and **(Boc)$_2$-2** (42 mg, 89 μmol) were dissolved in anhydrous CH_2Cl_2 (2.5 mL) containing dried molecular sieves 3 Å (50 mg, powder form) in a 20 mL vial under argon. A solution of piperidine/acetic acid in CH_2Cl_2 (550 μL, 60 mM/60 mM, 33 μmol/33 μmol) was added, and the mixture was stirred at room temperature for 20 h. The mixture was filtered through a Celite pad. The filtrate was concentrated and purified by chromatography [silica, hexanes/ethyl acetate (4:1 to 2:1, then 0:1)] to afford a dark-red gum (42 mg, 64%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 6H), 1.49 (s, 9H), 1.52 (s, 9H), 2.38 (s, 3H), 2.53 (s, 2H), 3.80 (s, 3H), 4.37 (s, 2H), 5.78 (d, *J* = 3.8 Hz, 1H), 6.14 (s, 1 H), 6.26 (t, *J* = 2.7 Hz, 1 H), 6.32 (d, *J* = 1.9 Hz, 1H), 6.88 (t, *J* = 2.7 Hz, 1H), 7.00 (d, *J* = 3.8 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 2H), 7.29−7.31 (d, *J* = 8.0 Hz, 2H), 7.62 (s, 1H), 7.76 (d, *J* = 2.0 Hz), 9.99 (s, 1H), 10.51 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.1, 27.7, 27.7, 29.0, 29.3, 41.6, 50.7, 52.9, 85.9, 86.0, 109.2, 109.4, 111.3, 112.5, 121.1, 121.2, 125.8, 126.8, 127.1, 127.5, 128.5, 129.2, 133.7, 133.9, 135.0, 135.1, 135.6, 136.3, 139.7, 148.2, 148.8, 160.6, 164.9, 166.0, 180.8, 188.7; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{43}H_{49}N_4O_8$ 749.3545, found 749.3548; λ_{abs} (CH_3CN) = 295 nm, 501 nm.

3-[7-(4-Bromophenyl)-2,3-dihydro-3,3-dimethyldipyrrin-1-yl]-2-carbomethoxy-1-(1-formyldipyrromethan-8-yl)prop-2-ene-1-one (20). Following a reported procedure,[19] a mixture of **18** (33 mg, 0.11 mmol), **2** (26 mg, 95 μmol), and dried molecular sieves 3 Å (26 mg, powder form) in a 20 mL vial under argon was treated with a solution of piperidine/acetic acid in CH_2Cl_2 (2.4 mL, 15 mM/15 mM, 144 μmol/144 μmol). The mixture was stirred at room temperature for 20 h, and then filtered through a Celite pad. The filtrate was concentrated and purified by chromatography [silica, hexanes/ethyl acetate (4:1)] to give a red gum as a mixture of isomers (20 mg, 34%). The absorption spectrum was collected at room temperature: λ_{abs} (CH_3CN) 295 nm (3.0 × 10^4 M^{-1} cm^{-1}), 487 nm (1.3 × 10^4 M^{-1} cm^{-1}). Further purification by reversed-phase TLC [silica with C18, 0.15 mm, 20 cm × 20 cm, methanol/H_2O (8:1)] gave the separated isomers, with the major component denoted ***Z*-20**

(R_f = 0.50, 17 mg, 29%) and the minor component denoted putative ***E*-20** (R_f = 0.40, 2.0 mg, 4%). Data for ***Z*-20**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 6H), 2.52 (s, 2H), 3.78 (s, 3H), 4.00 (s, 2H), 6.02 (s, 1H), 6.18−6.20 (m, 1H), 6.23 (t, J = 2.7 Hz, 1H), 6.52−6.54 (m, 1H), 6.85 (t, J = 2.7 Hz, 1H), 6.98−7.00 (m, 1H), 7.21−7.23 (m, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.60 (s, 1H), 9.31 (s, 1H), 9.98 (br, 1H), 10.66 (br, 1H), 11.04 (br, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 26.4, 28.9, 41.5, 50.5, 52.9, 106.9, 108.0, 109.1, 111.3, 119.7, 121.0, 125.0, 125.1, 125.8, 126.0, 127.4, 130.1, 130.6, 131.6, 132.2, 134.5, 135.5, 137.9, 140.8, 161.4, 165.4, 167.6, 179.1, 188.3; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{32}H_{30}N_4O_4Br$, 613.1445, found 613.1447. Data for ***E*-20**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 6H), 2.69 (s, 2H), 3.85 (s, 3H), 4.05 (s, 2H), 6.11 (s, 1H), 6.22−6.25 (m, 1H), 6.28 (t, J = 2.7 Hz, 1H), 6.55−6.59 (m, 1H), 6.94 (t, J = 2.7 Hz, 1H), 7.00−7.02 (m, 1H), 7.25 (s, 1H), 7.28 (d, J = 8.3 Hz, 2H), 7.38−7.40 (m, 1H), 7.52 (d, J = 8.3 Hz, 2H), 9.39 (s, 1H), 9.61 (br, 1H), 10.60 (br, 1H), 10.77 (br, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 26.4, 29.1, 41.6, 50.2, 52.8, 108.1, 108.3, 109.3, 111.1, 119.8, 120.9, 124.3, 124.3, 125.1, 125.6, 126.0, 127.4, 129.9, 130.2, 131.6, 132.4, 132.9, 135.6, 139.2, 161.3, 167.7, 179.1, 184.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{32}H_{30}N_4O_4Br$ 613.1445, found 613.1449.

2-Carbomethoxy-3-[2,3-dihydro-3,3-dimethyl-7-(4-bromophenyl)-dipyrrin-1-yl]-1-[10,11-bis(*N-tert*-butoxycarbonyl)-1-formyldipyrromethan-8-yl]prop-2-ene-1-one ((Boc)$_2$-20). Reaction of **18** (86 mg, 0.23 mmol) and **(Boc)$_2$-2** (100. mg, 0.210 mmol) under the general procedure described for **(Boc)$_2$-19** followed by chromatography [silica, hexanes/ethyl acetate (3:1 then 1:2)] gave a dark-red gum (85 mg, 50%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 6H), 1.49 (s, 9H), 1.52 (s, 9H), 2.55 (s, 2 H), 3.81 (s, 3H), 4.37 (s, 2H), 5.78 (d, J = 3.8 Hz, 1H), 6.05 (s, 1H), 6.24 (t, J = 2.7 Hz, 1H), 6.32 (d, J = 1.9 Hz, 1H), 6.88 (t, J = 2.7 Hz, 1H), 7.00 (d, J = 3.7 Hz, 1H), 7.26 (d, J = 8.1 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.61 (s, 1H), 7.76 (d, J = 2.0 Hz, 1H), 9.99 (s, 1H), 10.54 (s, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 27.7, 27.7, 28.9, 29.2, 41.6, 50.8, 52.9, 85.9, 86.1, 108.5, 109.2, 111.3, 112.4, 119.8, 121.1, 121.2, 125.3, 125.7, 127.2, 127.4, 130.1, 131.6, 133.9, 134.7, 135.1, 135.6, 136.8, 139.7, 148.2, 148.8, 161.1, 164.8, 166.7, 180.7, 188.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{42}H_{46}BrN_4O_8$ 813.2494, found 813.2493; λ_{abs} (CH_3CN) = 295 nm, 493 nm.

33-[7-(4-Bromophenyl)-2,3-dihydro-3,3-dimethyldipyrrin-1-yl]-2-carbomethoxy-1-[5-(3,5-dimethylphenyl)-1-formyldipyrromethan-8-yl]prop-2-ene-1-one (21). Reaction of **18** (22 mg, 61 μmol) and **15** (21 mg, 55 μmol) under the general procedure described for **(Boc)$_2$-19** followed by preparative TLC [silica, 1 mm thick, hexanes/ethyl acetate (3:1)] afforded two red bands. The two bands were collected together. Further preparative TLC [silica, 1 mm thick, 20 cm × 20 cm, hexanes/ethyl acetate (3:2)] for 2 h afforded (i) a minor purple-red band [R_f = 0.30, hexanes/ethyl acetate (3:2) after 2 h purification], which was collected as a red gum of putative ***E*-21** (2.4 mg, 6%), and (ii) a major red band [R_f = 0.25, hexanes/ethyl acetate (3:2)], which was collected as a red gum of putative ***Z*-21** (15 mg, 38%). Data for putative ***E*-21**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.21 (s, 6H), 2.30 (s, 6H), 2.69 (s, 2H), 3.35 (s, 1H), 3.83 (s, 3H), 5.40 (s, 1H), 6.11 (s, 1H), 6.15 (t, J = 3.2 Hz, 1H), 6.28 (t, J = 2.8 Hz, 1H), 6.48 (s, 1H), 6.80 (s, 2H), 6.93 (t, J = 3.2 Hz, 1H), 6.95 (t, J = 2.7 Hz, 1H), 6.97 (s, 1H), 7.29 (s, 1H), 7.31 (s, 1H), 7.41 (d, J = 2.6 Hz, 1H), 7.52 (s, 1H), 7.53 (s, 1H), 8.40 (br s, 1H), 9.08 (br s, 1H), 9.41 (s, 1H), 10.76 (br s, 1H); ^{13}C{^{1}H} NMR (MHz, $CDCl_3$) δ 21.4, 29.1, 41.6, 43.9, 50.2, 52.8, 108.2, 108.4, 109.0, 109.3, 109.9, 110.9, 119.8, 120.9, 124.4, 125.1, 125.3, 126.1, 126.9, 127.5, 129.9, 130.2, 131.6, 132.6, 133.0, 133.5, 139.0, 139.1, 140.7, 147.3, 161.3, 167.7, 178.8 (one carbon signal was not detected, perhaps due to the small quantity of sample); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{40}H_{38}BrN_4O_4$, 717.2071, found 717.1069; data for putative ***Z*-21**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.07 (d, J = 2.0 Hz, 6H), 2.21 (s, 6H), 2.54 (s, 2H), 3.80 (s, 3H), 5.37 (s, 1H), 6.05 (s, 1H), 6.08 (dd, J_1 = 3.9 Hz, J_2 = 2.5 Hz, 1H), 6.24 (t, J = 2.7 Hz, 1H), 6.46 (t, J = 2.2 Hz, 1H), 6.68 (d, J = 1.7 Hz, 2H), 6.85 (t, J = 2.7 Hz, 1H), 6.87 (dd, J_1 = 3.9 Hz, J_2 = 2.4 Hz, 1H), 6.91 (s, 1H), 7.24 (dd, J_1 = 3.2 Hz, J_2 = 1.7 Hz, 1H), 7.26−7.26 (m, 2H), 7.27 (s, 1H), 7.50 (s, 1H), 7.51 (s, 1H), 7.61 (s, 1H), 8.77 (br s, 1H), 9.24 (s, 1H), 9.48 (br s, 1H), 10.67 (br s, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 21.3, 28.9, 41.6, 43.7, 50.6, 52.9, 107.9, 108.2, 109.2, 111.2, 120.0, 121.2, 122.4, 125.1, 125.7, 126.0, 126.0, 127.4, 129.7, 130.2, 131.6, 132.6, 134.1, 134.7, 135.7, 137.8, 138.8, 138.9, 141.3, 161.3, 165.3, 167.4, 178.8, 188.3; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{40}H_{38}BrN_4O_4$ 717.2071, found 717.2067.

In(III)Cl-2-*p*-tolyl-13^2-carbomethoxy-18,18-dimethyl-13^1-oxophorbine (22). A solution of **19** (34 mg, 62 μmol) in acetonitrile (ACS grade, 310 mL) was treated with $In(OTf)_3$ (349 mg, 0.620 mmol) and $InCl_3$ (137 mg, 0.620 mmol). The mixture was stirred at 80 °C in an oil bath in the presence of air with monitoring by absorption spectroscopy. After 20 h, the reaction mixture was allowed to cool to room temperature whereupon Et_3N (0.5 mL) was added. The reaction mixture was filtered. The filtrate was concentrated to a dark-brown oil and purified by chromatography [silica, ethyl acetate to methanol/ethyl acetate (1:3)] to afford a green film (2.0 mg, 4.9%, mixture of diastereomers): ^{1}H NMR (600 MHz, $CDCl_3$) δ major product: 2.05 (s, 3H), 2.24 (s, 3H), 2.63 (s, 6H), 3.39−4.33 (m, 1H), 4.60−4.75 (m, 1H), 5.10−5.11 (m, 1H), 7.61 (d, J = 2.7 Hz, 2H), 8.04 (d, J = 2.3 Hz, 2H), 8.85 (s, 1H), 9.01 (s, 1H), 9.12 (s, 1H), 9.17−9.18 (m, 1H), 9.41 (s, 1H), 9.65 (s, 1H), 10.01 (s, 1H); δ minor product: 2.05 (s, 3H), 2.24 (s, 3H), 2.63 (s, 6H), 3.87−4.25 (m, 1H), 4.91−5.01 (m, 1H), 5.12−5.13 (m, 1H), 7.62 (d, J = 2.5 Hz, 2H), 8.05 (d, J = 2.3 Hz, 2H), 8.87 (s, 1H), 9.02 (s, 1H), 9.13 (s, 1H), 9.17 (m, 1H), 9.41 (s, 1H), 9.66 (s, 1H), 10.05 (s, 1H); poor solubility precluded obtaining a ^{13}C NMR spectrum; HRMS (ESI-TOF) m/z [M − Cl]$^+$ calcd for $C_{33}H_{26}InN_4O_3$ 641.1038, found 641.1045; λ_{abs} (CH_3CN) = 419 nm, 647 nm.

In(III)Cl-2-(4-Bromophenyl)-13^2-carbomethoxy-18,18-dimethyl-13^1-oxophorbine (23). A solution of **20** (20. mg, 32 μmol) in acetonitrile (ACS grade, 150 mL) was treated with $In(OTf)_3$ (180 mg, 0.32 mmol) and $InCl_3$ (71 mg, 0.32 mmol) and stirred at 80 °C in an oil bath for 20 h under air. The progress of the reaction was monitored by absorption spectroscopy. Then the reaction mixture was allowed to cool to room temperature whereupon excess Et_3N (0.5 mL) was added. The reaction mixture was concentrated and purified by chromatography [silica, CH_2Cl_2/ethyl acetate (3:1)] to afford a green solid (3.0 mg, 13%, a mixture of diastereomers): ^{1}H NMR (300 MHz, $CDCl_3$) δ major product: 1.95 (s, 3H), 2.08 (s, 3H), 3.08 (s, 3H), 4.10−4.22 (AB, J = 17.3 Hz, 2H), 6.31 (s, 1H), 7.93 (d, J = 8.5 Hz, 2H), 8.00 (d, J = 8.6 Hz, 2H), 8.69 (s, 1H), 8.94−8.97 (m, 1H), 9.08−9.14 (m, 2H), 9.31 (s, 1H), 9.60 (s, 1H), 9.94 (s, 1H); minor product: 1.79 (s, 3H), 2.19 (s, 3H), 3.96 (s, 3H), 4.18−4.57 (AB, J = 17.3 Hz, 2H), 5.96 (s, 1H), 7.93 (d, J = 8.5 Hz, 2H), 8.00 (d, J = 8.6 Hz, 2H), 8.67 (s, 1H), 8.94−8.97 (m, 1H), 9.08−9.14 (m, 2H), 9.29 (s, 1H), 9.60 (s, 1H), 9.93 (s, 1H); poor solubility precluded obtaining a ^{13}C NMR spectrum; HRMS (ESI-TOF) m/z [M − Cl]$^+$ calcd for $C_{32}H_{23}N_4O_3BrIn$ 704.9992, found 704.9964; λ_{abs} (CH_3CN) = 423, 651 nm; MALDI-MS (4-CHCA) calcd for $C_{32}H_{23}N_4O_3BrClIn$ 739.968, found 740.617.

In(III)Cl-2-(4-Bromophenyl)-10-(3,5-dimethylphenyl)-13^2-carbomethoxy-18,18-dimethyl-13^1-oxophorbine (24). A solution of **21** (10.0 mg, 13.9 μmol) in acetonitrile (ACS grade, 65 mL) was treated with $In(OTf)_3$ (78.0 mg, 139 μmol) and $InCl_3$ (30.8 mg, 139 μmol) and stirred at 80 °C in an oil bath for 20 h under air in the dark. Then the reaction mixture was allowed to cool to room temperature whereupon Et_3N was added. The reaction mixture was passed through a Celite pad, and the filtrate was concentrated and purified by preparative TLC [silica, 1 mm thick, 20 cm × 20 cm, R_f = 0.22 in hexanes/ethyl acetate (1:1), hexanes/ethyl acetate (1:1)] to afford a green film (5.8 mg, 49%, a mixture of diastereomers): ^{1}H NMR (600 MHz, $CDCl_3$) δ major product: 1.94 (s, 3H), 2.06 (s, 3H), 2.17 (s, 1H), 2.61 (s, 6H), 3.86 (s, 3H), 4.08−4.11 (m, 1H), 4.33−4.36 (1H), 6.23 (s, 1H), 7.88−7.94 (m, 3H), 7.99−8.01 (m, 3H), 8.59 (s, 1H), 8.77 (dd, J_1 = 4.4 Hz, J_2 = 3.3 Hz, 2H), 8.96 (s, 1H), 9.05 (s, 1H), 9.51 (s, 1H); δ minor product: 1.89 (s, 3H), 2.05 (s, 3H), 2.14 (s, 1H), 2.56 (s, 6H), 3.93 (s, 3H), 4.11−4.19 (m, 1H), 4.46−4.49 (m, 1H), 5.93 (s, 1H), 7.92−7.94 (m, 3H), 7.99−8.01 (m, 3H), 8.56 (s, 1H), 8.82–8.84 (m, 2H), 8.90 (s, 1H), 9.04 (s, 1H), 9.50 (s, 1H); poor solubility precluded obtaining a ^{13}C NMR spectrum; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{40}H_{32}BrClInN_4O_3$ 845.0380, found 845.0379; λ_{abs} (CH_3CN) = 429 nm, 651 nm; MALDI-MS (4-CHCA) calcd for $C_{40}H_{31}BrInN_4O_3$ 809.062, found 810.434.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.9b02770.

Tables of additional reaction investigations; X-ray data for **2**, **8**, and **9-Br**; absorption spectral data for **19**–**21**; fluorescence spectra for **22**–**24**; NOESY data and conformational diagrams of isomers of **20**; and ^{1}H and ^{13}C NMR spectra for all compounds (PDF)

Crystallographic information for compound **2** (CIF)

Crystallographic information for compound **8** (CIF)

Crystallographic information for compound **9-Br** (CIF)

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Notes

The authors declare no competing financial interest.

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