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Expanded Scope of Synthetic Bacteriochlorins via Improved Acid Catalysis Conditions and Diverse Dihydrodipyrrin-Acetals

Michael Krayer, Marcin Ptaszek, Han-Je Kim, Kelly R. Meneely, Dazhong Fan, Kristen Secor, and Jonathan S. Lindsey*

Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204

jlindsey@ncsu.edu

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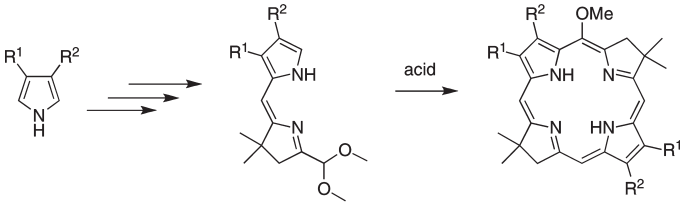

a dihydrodipyrrin-acetal a 5-methoxybacteriochlorin

Bacteriochlorins are attractive candidates for a wide variety of photochemical studies owing to their strong absorption in the near-infrared spectral region. The prior acid-catalysis conditions [$BF_3 \cdot O(Et)_2$ in CH_3CN at room temperature] for self-condensation of a dihydrodipyrrin-acetal (bearing a geminal dimethyl group in the pyrroline ring) typically afforded a mixture of three macrocycles: the expected 5-methoxybacteriochlorin (**MeOBC**-type), a 5-unsubstituted bacteriochlorin (**HBC**-type), and a free base B,D-tetradehydrocorrin (**TDC**-type). Here, a broad survey of >20 acids identified four promising acid catalysis conditions of which TMSOTf/2,6-di-*tert*-butylpyridine in CH_2Cl_2 at room temperature was most attractive owing to formation of the 5-methoxybacteriochlorin as the sole macrocycle regardless of the pyrrolic substituents in the dihydrodipyrrin-acetal (electron-withdrawing, electron-donating, or no substituent). Eleven new dihydrodipyrrin-acetals were prepared following standard routes. Application of the new acid catalysis conditions has afforded diverse bacteriochlorins (e.g., bearing alkyl/ester, aryl/ester, diester, and no substituents) in a few days from commercially available starting materials. Consideration of the synthetic steps and yields for formation of the dihydrodipyrrin-acetal and bacteriochlorin underpins evaluation of synthetic plans for early installation of bacteriochlorin substituents via the dihydrodipyrrin-acetal versus late installation via derivatization of β-bromobacteriochlorins. Treatment of the 5-methoxybacteriochlorins with NBS gave regioselective 15-bromination when no pyrrolic substituents were present or when each pyrrole contained two substituents; on the other hand, the presence of a β-ethoxycarbonyl group caused loss of regioselectivity. The 15 new bacteriochlorins prepared herein exhibit a long-wavelength absorption band in the range 707−759 nm, providing tunable access to the near-infrared region. Taken together, this study expands the scope of available bacteriochlorins for fundamental studies and diverse applications.

Introduction

Bacteriochlorins, tetrahydroporphyrins containing alternating pyrrole and pyrroline rings, are distinguished from other members of the tetrapyrrole family of macrocycles by the presence of an intense ($\varepsilon \sim 10^5\ M^{-1}cm^{-1}$) long-wavelength absorption band located in the near-infrared region (700−900 nm).[1] The near-infrared (NIR) absorption band opens the door to photochemical studies with light of lower energy than that in the ultraviolet or visible regions, and enables capture of the large fraction of solar light in the NIR spectral region.[2] In

(1) Kobayashi, M.; Akiyama, M.; Kano, H.; Kise, H. In *Chlorophylls and Bacteriochlorophylls: Biochemistry, Biophysics, Functions and Applications*; Grimm, B., Porra, R. J., Rüdiger, W., Scheer, H., Eds.; Springer: Dordrecht, The Netherlands, 2006; pp 79−94.

(2) Stromberg, J. R.; Marton, A.; Kee, H. L.; Kirmaier, C.; Diers, J. R.; Muthiah, C.; Taniguchi, M.; Lindsey, J. S.; Bocian, D. F.; Meyer, G. J.; Holten, D. *J. Phys. Chem. C* **2007**, *111*, 15464–15478.

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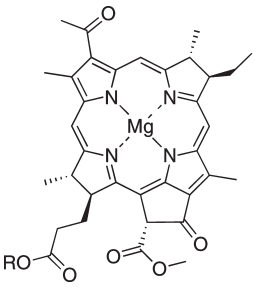
this regard, bacteriochlorophylls *a*, *b*, and *g* contain the bacteriochlorin chromophore and provide the basis for light-harvesting processes and electron-transfer reactions in bacterial photosynthesis (Chart 1).[3] While the biosynthesis[4] and spectroscopy[1] of bacteriochlorophylls remain fertile areas of investigation, the synthetic chemistry of bacteriochlorins is relatively undeveloped.[5−7] The development of robust and versatile routes for preparing and modifying bacteriochlorin macrocycles is essential for fundamental studies of their chemical and physical properties and understanding the intricacies of their roles in photosynthetic processes.

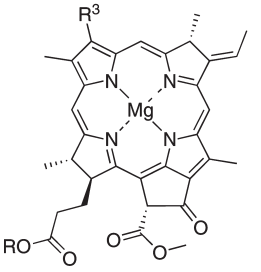
The ability to tailor synthetic bacteriochlorins with peripheral substituents should enable a host of important properties to be tuned in a systematic manner. The properties include the following: (i) the position of the near-infrared absorption band, (ii) redox potentials, (iii) metal chelate stability, (iv) solubility, (v) supramolecular interactions including self-assembly, and (vi) amenability as constituents in diverse photochemical applications ranging from artificial photosynthesis to medicine. One approach to the synthesis of bacteriochlorins relies on semisynthesis, namely modification of existing bacteriochlorophylls.[5,7] A second approach entails reduction or derivatization of porphyrins or chlorins.[5] Both approaches have merit but both lack the potential versatility of de novo synthetic routes wherein the bacteriochlorin chromophore is constructed directly from acyclic precursors. For example, the fully unsubstituted bacteriochlorin (lacking β-pyrrole substituents) is a key benchmark for all spectroscopic and photochemical studies of bacteriochlorophylls, yet has hardly been investigated.[8] Similarly, incorporation of bacteriochlorins into multipigment arrays to explore energy- and electron-transfer reactions, as has been done vigorously with porphyrins,[9] has been comparatively untouched.[10] The dearth of such studies stems from synthetic limitations in the creation of suitable bacteriochlorin macrocycles.

Over the past few years we have been working to develop a synthetic route to bacteriochlorins. The route entails the acid-catalyzed self-condensation of a dihydrodipyrrin-acetal, wherein the pyrroline ring contains a geminal dimethyl group integral to the ring and the acetal moiety located at the α-position. The first dihydrodipyrrin-acetal examined (**1-T**) contained a *p*-tolyl group attached to the β-pyrrole ring (R^1 = *p*-tolyl, R^2 = H). Treatment of **1-T** with $BF_3 \cdot O(Et)_2$ in CH_3CN afforded a mixture of two free base bacteriochlorins (**HBC-T**, **MeOBC-T**) and a free base B,D-tetradehydrocorrin (**TDC-T**) (Scheme 1).[11] Each macrocycle contains a geminal dimethyl group in each pyrroline ring, which makes these compounds oxidatively stable under routine handling. By contrast, bacteriochlorophylls derived from photosynthetic bacteria are prone to adventitious dehydrogenation upon handling outside of their natural physiological environment, giving rise to chlorins and/or porphyrins.[12]

CHART 1



Bacteriochlorophyll *a*



Bacteriochlorophyll *b* (R^3 = acetyl)
Bacteriochlorophyll *g* (R^3 = vinyl)

The formation of three macrocycles from the self-condensation was both a limitation of the synthetic route and an opportunity to access distinct compounds. Alteration of the concentrations of the acid [$BF_3 \cdot O(Et)_2$ from 10−500 mM] and the acetal (**1-T** from 2.5−50 mM) was found to shift the product distribution considerably. Indeed, distinct conditions were identified that would favor a given macrocycle, with isolation of a much lesser quantity of one of the other macrocycles: the preparative synthesis with 18 mM **1-T** and 140 mM $BF_3 \cdot O(Et)_2$ gave predominantly **HBC-T** (49%); 5 mM **1-T** and 50 mM $BF_3 \cdot O(Et)_2$ gave predominantly **MeOBC-T** (30%); and 11 mM **1-T** and 10 mM $BF_3 \cdot O(Et)_2$ gave predominantly **TDC-T** (66%).[11] A study reported here showed that the yield of **MeOBC-T** was increased to 46% upon use of 18 mM **1-T** and 45 mM $BF_3 \cdot O(Et)_2$, but the product was accompanied by **HBC-T** and **TDC-T** in yields of 6% and 11%, respectively (see Supporting Information). Nevertheless, conditions that afford a single macrocycle in good yield have heretofore not been identified.

The self-condensation route, developed upon examination of the synthesis of 2,12-di-*p*-tolylbacteriochlorins,[11] has been extended to other dihydrodipyrrin-acetals to afford

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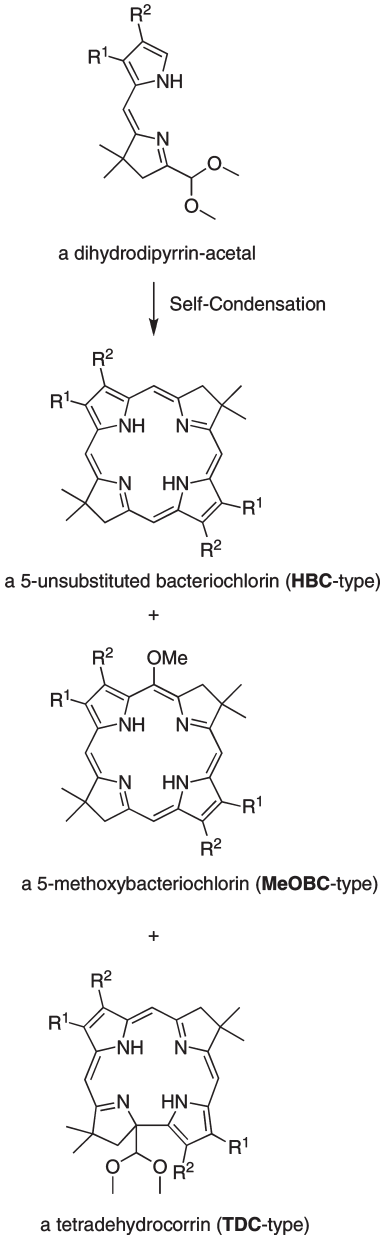
(11) Kim, H.-J.; Lindsey, J. S. *J. Org. Chem.* **2005**, *70*, 5475–5486.
(12) (a) Limantara, L.; Koehler, P.; Wilhelm, B.; Porra, R. J.; Scheer, H. *Photochem. Photobiol.* **2006**, *82*, 770–780. (b) Kozyrev, A. N.; Chen, Y.; Goswami, L. N.; Tabaczynski, W. A.; Pandey, R. K. *J. Org. Chem.* **2006**, *71*, 1949–1960.

SCHEME 1. Self-Condensation of a Dihydrodipyrrin-Acetal Resulting in Three Macrocycles



bacteriochlorins bearing 3,13-dibromo,[8] 2,12- or 3,13-bis-(swallowtail) [$CH(CH_2CH_2OCH_3)_2$],[13] or 3,13-dimesityl substituents.[14] Application of the conditions identified with **1-T** gave uneven results with these other dihydrodipyrrin-acetals. For example, treatment of the bromodihydrodipyrrin-acetal (**1-Br**, R^1 = H, R^2 = Br) at 5 mM with 50 mM $BF_3 \cdot O(Et)_2$ gave **HBC-Br** as the predominant macrocycle and only in 15% yield. Similar low yields also were obtained with the other dihydrodipyrrin-acetals. The ability to obtain a single target macrocycle in reasonable yield is essential for progress in bacteriochlorin chemistry. Given the known sensitivity of tetrapyrrole macrocycle formation to the nature and concentration of acid catalysts,[15] and the expected strong influence of substituents attached to the pyrrole nucleus in the dihydropyrrin-acetal unit, we embarked on a systematic study of the effects of acid catalysts on a basis set of substituted dihydrodipyrrin-acetals. A key issue was whether conditions could be identified that make use of acids milder than $BF_3 \cdot O(Et)_2$ yet form the **HBC-** or **MeOBC-**type bacteriochlorin in good yield and in selective fashion.

In this paper, we describe the study of reaction conditions for the self-condensation of dihydrodipyrrin-acetals to give bacteriochlorins. The paper is divided into three major parts. Part I describes the preparation of a collection of dihydrodipyrrin-acetals with electron-withdrawing, electron-donating, or no substituents at the R^1 and R^2 positions (Chart 2). Part II describes a two-tiered search for Lewis acids for the self-condensation of the dihydrodipyrrin-acetals. The first tier entailed a survey of >20 acids applied to the condensation of **1-T** and **1-Br**. From this broad ranging survey, four acids were identified that afforded promising results. The second tier applied the four acids to a basis set of dihydrodipyrrin-acetals, while systematically varying both the concentration of the dihydrodipyrrin-acetal and the acid. The results of this study provide access to new bacteriochlorins, provide insights into the reactivity of precursors to bacteriochlorins, and also inform synthetic planning for the preparation of substituted bacteriochlorins either by prefunctionalizing the precursors to bacteriochlorins or by introducing substituents in intact bacteriochlorin macrocycles. Part III describes a bromination study of three new **MeOBC-**type bacteriochlorins, which were readily accessed through the methods developed herein.

Results

I. Synthesis of Dihydrodipyrrin-Acetals. The generic synthesis of dihydrodipyrrin-acetals entails five steps from a pyrrole as shown in Scheme 2. The steps include formylation to give the pyrrole-2-carboxaldehyde (**2**), nitro-aldol (Henry) condensation to give the nitrovinylpyrrole and subsequent reduction to give the 2-(2-nitroethyl)pyrrole (**3**), Michael addition with the α,β-unsaturated ketone-acetal **4**[11] to give the nitrohexanone-pyrrole (**5**), and McMurry-type ring closure to give the dihydrodipyrrin-acetal (**1**). Since the first synthesis of the *p*-tolyl-substituted dihydrodipyrrin-acetal **1-T**,[11] considerable effort has been devoted to the development of improved and general procedures for this overall transformation. The key improvements include smooth conditions for installing the nitroethyl group,[16] a solventless method for the Michael addition,[17] and mild conditions for forming the pyrroline ring;[18] all of these are carried out with limited chromatography so as to enable synthesis at the multigram scale.[18] Such methods were developed largely for a scalable synthesis of the known[8] **1-Br** and have been applied herein

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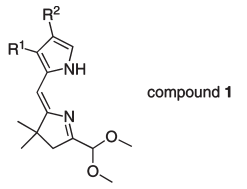
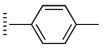
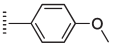
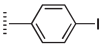
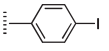
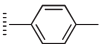
CHART 2. Dihydrodipyrrin-Acetals for the Self-Condensation to Bacteriochlorins

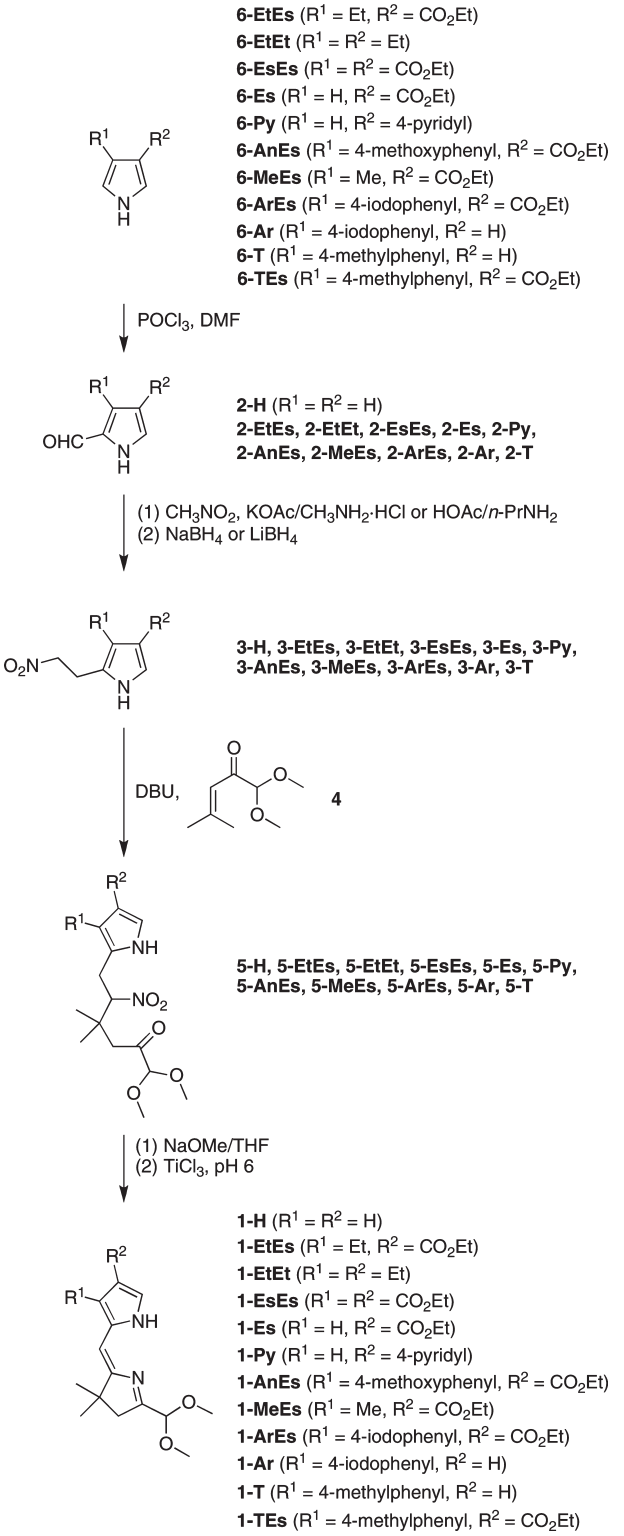


Compound **1**	R^1	R^2
1-T		–H
1-Br	–H	–Br
1-H	–H	–H
1-EtEs	–Et	$-CO_2Et$
1-EtEt	–Et	–Et
1-EsEs	$-CO_2Et$	$-CO_2Et$
1-Es	–H	$-CO_2Et$
1-Py	–H	
1-AnEs		$-CO_2Et$
1-MeEs	$-CH_3$	$-CO_2Et$
1-ArEs		$-CO_2Et$
1-Ar		–H
1-TEs		$-CO_2Et$

where possible for the synthesis of the dihydrodipyrrin-acetals. In this regard, a refined synthesis of known dihydrodipyrrin-acetals **1-T**[11] and **1-H**[17] at substantial scale (> 350 mg) has been carried out.

The synthesis of each dihydrodipyrrin-acetal begins with a corresponding pyrrole. Pyrroles **6-EtEt**,[19] **6-Py**,[20] **6-AnEs**,[21] **6-MeEs**,[22] **6-ArEs**,[23] **6-Ar**,[24] and **6-TEs**[11] were prepared according to the literature, whereas **6-EsEs** was obtained commercially. Dihydrodipyrrin-acetal **1-EtEs** required the

SCHEME 2. Synthesis of Dihydrodipyrrin-Acetals



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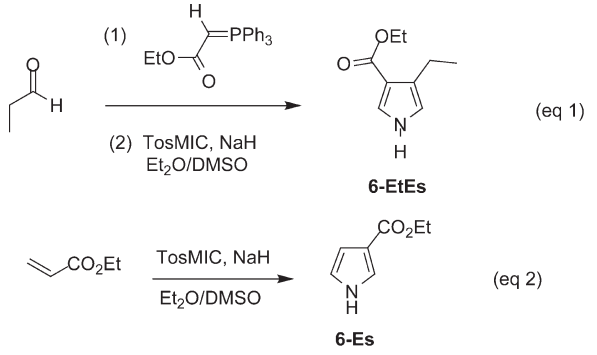
synthesis of pyrrole **6-EtEs**. The Wittig reaction of propionaldehyde and (carbethoxymethylene)triphenylphosphorane (following a procedure for a methyl homologue)[25] afforded the corresponding α,β-unsaturated esters, which upon treatment with *p*-toluenesulfonyl methylisocyanide (TosMIC) via the van Leusen method[26] gave pyrrole **6-EtEs** (eq 1). Similar treatment of ethyl acrylate with TosMIC gave pyrrole **6-Es** (eq 2).



The synthesis of each dihydrodipyrrin-acetal generally followed established methods; however, the conditions for each synthetic step (especially time and temperature) can vary considerably due to the different reactivity imparted by the pyrrole substituents. Key observations concerning the synthesis of the various dihydrodipyrrin-acetals are as follows:

(i) Vilsmeier−Haack formylation proceeded at room temperature in 2−3 h for 3-(ethoxycarbonyl)-4-ethylpyrrole (**6-EtEs**) and 3,4-diethylpyrrole (**6-EtEt**), at room temperature overnight for 3-ethoxycarbonylpyrrole (**6-Es**) and 3-(4-pyridyl)pyrrole (**6-Py**), and at 80 °C for 24 h for 3,4-bis-(ethoxycarbonyl)pyrrole (**6-EsEs**). Formylation of the unsymmetrical pyrroles **6-EtEs**, **6-MeEs**, **6-Es**, and **6-Py** predominantly took place at the α-position distal to the ester or pyridyl substituent. A single-crystal X-ray structure of **2-Py** provided proof of regioselectivity of formylation (see the Supporting Information). The minor regioisomer (with substitution at the proximal α-position) was easily separated by column chromatography and was not further characterized. Note that formylpyrrole **2-Py** is poorly soluble in a variety of solvents, which made handling and purification difficult.

(ii) The formylpyrroles **2** were converted to nitroethylpyrroles **3** via the nitro-aldol condensation and subsequent reduction of the vinyl group. For the compounds containing ester substituents (**3-EtEs**, **3-EsEs**, and **3-Es**), the reduction was carried out using $NaBH_4$ instead of $LiBH_4$ to avoid possible reduction of the ester groups. Nitroethylpyrroles **3-EtEs**, **3-EsEs**, **3-Es**, and **3-Py** (containing electron-withdrawing substituents) were stable under routine handling and could be purified via column chromatography, while the electron-rich **3-EtEt** decomposed rapidly when subjected to silica or alumina column chromatography and was therefore used in crude form for the subsequent Michael addition.

(iii) The Michael addition reaction of **3** typically was carried out under solventless conditions for 16 h at room temperature using 1.2 equiv of the Michael acceptor **4** and DBU to afford the nitrohexanone-pyrrole **5**. The reaction of **3-EtEt** with 2 equiv of DBU for 5 h at room temperature gave **5-EtEt** in 29% yield, whereas **3-EsEs** with 10 equiv of **4** at room temperature for 15 min gave **5-EsEs** in 20% yield. Fewer equivalents and longer reaction times resulted in lower yields. The Michael addition of **3-Es** or **3-Py** was carried out using 3 equiv of **4** and 3 equiv of DBU for 1 h at room temperature to afford **5-Es** or **5-Py** in 66% or 27% yield, respectively.

(iv) Nitrohexanone-pyrroles **5** were converted to the dihydrodipyrrin-acetals **1** by reductive cyclization using NaOMe and a buffered solution of $TiCl_3$ at room temperature for 16 h, except for **5-Py**, which required longer reaction time (48 h) and higher temperature (35 °C). Dihydrodipyrrin-acetal **1-EtEt** was extremely unstable and began decomposing within a few minutes. Accordingly, complete characterization was not obtained for **1-EtEt**, and the attempted self-condensation studies did not result in significant bacteriochlorin formation (vide infra).

(v) Dihydrodipyrrin-acetal **1-TEs** was synthesized in a streamlined fashion from pyrrole **6-TEs** without characterization of all intermediates.

Each dihydrodipyrrin-acetal was characterized by ^1H NMR and ^{13}C NMR spectroscopy and by ESI-MS. Dihydrodipyrrin-acetals bearing electron-withdrawing substituents (e.g., CO_2Et) were stable and could be stored at −10 °C for several months. Dihydrodipyrrin-acetals bearing no substituents (**1-H**) or electron-donating substituents (**1-EtEt**) began decomposing within hours or minutes, respectively, and consequently were used immediately in the self-condensation reaction, typically after quick purification on an alumina column.

II. Acid Catalysis Conditions for Bacteriochlorin Formation. Bacteriochlorin formation (Scheme 1) requires reaction of the nucleophilic α-pyrrolic position and the electrophilic acetal moiety of the dihydrodipyrrin-acetal. The **MeOBC**-type macrocycles form solely by condensation processes whereas an unknown reduction step ($2e^-/2H^+$) occurs to give the **HBC**-type macrocycles.[11] A chief goal here was to find broadly applicable conditions that selectively afford a single bacteriochlorin macrocycle rather than a mixture of the **MeOBC**-type and **HBC**-type macrocycles. The acid likely serves to increase the electrophilicity of the acetal carbon. In this regard, the acid catalysis is expected to resemble the well-known acid-mediated hydrolysis of acetals as well as the Mukaiyama aldol condensation of acetals and silyl ethers.[27] Accordingly, in the initial broad survey we focused mainly on Lewis acids that are reported to be active in acetal hydrolysis and Mukaiyama aldol condensations. Mild acid catalysts known to afford superior results in reactions leading to porphyrins also were examined.[15]

1. Broad Survey of Acid Catalysts. The previous study employed dihydrodipyrrin-acetal **1-T** at 2.5−50 mM and $BF_3 \cdot O(Et)_2$ at 10−500 mM in CH_3CN, catalysis conditions that emerged from a short survey of a set of acids all in

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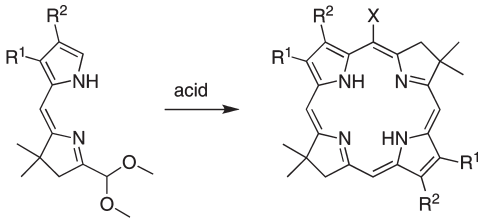
TABLE 1. Lewis Acids Identified from the Self-Condensation Survey of 1-T and 1-Br[a]



a dihydrodipyrrin-acetal X = H or MeO

1	R^1	R^2	acid	time (h)	**HBC-T** (%)	**MeOBC-T** (%)
1-T	*p*-tolyl	H	$Bi(OTf)_3$	19	7.6	32
1-T	*p*-tolyl	H	$Hf(OTf)_4 \cdot xH_2O$	19	13	28
1-T	*p*-tolyl	H	$HfCl_4$	15	1.5	18
1-T	*p*-tolyl	H	TMSOTf/2,6-DTBP[b]	13	-[c]	17

1	R^1	R^2	acid	time (h)	**HBC-Br** (%)	**MeOBC-Br** (%)
1-Br	H	Br	$Bi(OTf)_3$	19	30	6.5
1-Br	H	Br	$Hf(OTf)_4 \cdot xH_2O$	16	33	trace[d]
1-Br	H	Br	$HfCl_4$	16	-[c]	-[c]
1-Br	H	Br	TMSOTf/2,6-DTBP[b]	13	-[c]	25

[a]All reactions were carried out in CH_2Cl_2 at room temperature with 10 mM **1-T** or **1-Br**, and 50 mM acid. Yields were determined by absorption spectroscopy of samples isolated by chromatography (limit of detection ~0.4%). [b]50 mM TMSOTf and 500 mM 2,6-DTBP. [c]Not detected. [d]Observed in small quantity by TLC but no yield determined.

CH_3CN.[11] Here, >20 Lewis acids[28,29] were investigated for the self-condensation of **1-T** in solvents less polar than CH_3CN, such as CH_2Cl_2 or toluene. The reactions were conducted with 10 mM dihydrodipyrrin-acetal (0.02 or 0.03 mmol scale) and 50 mM acid. The reactions were followed by TLC and UV−vis spectroscopy. Reactions that showed at least traces of bacteriochlorin in the crude reaction mixture by UV−vis spectroscopy (Q_y absorption >700 nm) were quenched by the addition of TEA. Bacteriochlorins were isolated by chromatography, whereupon yields were determined spectroscopically [assuming $\varepsilon_{Qy} = 130000\ M^{-1}\ cm^{-1}$ and $\varepsilon_{Qy} = 120000\ M^{-1}\ cm^{-1}$ for **HBC**-type and **MeOBC**-type bacteriochlorins, respectively].[11] The acids were grouped as follows on the basis of the results with **1-T** in CH_2Cl_2 for up to 48 h at room temperature: (a) little reaction occurred and starting material was recovered [$Sn(OAc)_4$, $Al(acac)_3$, LiOTf]; (b) the starting material was consumed but little or no macrocycle formation was observed [$Cu(OTf)_2$, $ZrCp_2Cl_2$, $Pd(O_2CCF_3)_2$, Bu_2GeCl_2, $AlMe_3$, TMSOTf]; (c) **TDC-T** was predominantly formed [$Dy(OTf)_3$, $Eu(OTf)_3$, $Pr(OTf)_3$, $Er(OTf)_3$, $Yb(NTf_2)_3$, $Ga(OTf)_3$, $In(OTf)_3$]; and (d) **HBC-T** or **MeOBC-T** was formed in >5% yield [$Sn(OTf)_2$, $Bi(OTf)_3$, $Hf(OTf)_4 \cdot xH_2O$, $HfCl_4$, TMSOTf/2,6-di-*tert*-butylpyridine (2,6-DTBP)[30]].

An extension of this survey to **1-Br** gave the same general grouping of acids, although a number of the active catalysts (except TMSOTf/2,6-DTBP) tended to give the **HBC**- versus the **MeOBC**-type macrocycle. On the basis of the broad survey of acid catalysts with **1-T** and **1-Br**, the best conditions identified for bacteriochlorin formation are summarized in Table 1. Among the catalysts, TMSOTf/2,6-DTBP appeared superior given that this catalyst system afforded exclusively the 5-methoxybacteriochlorin. Indeed, the dibromobacteriochlorin **MeOBC-Br** is a new compound, as this was not obtained previously[8] via $BF_3 \cdot O(Et)_2$ catalysis.

A number of other studies were carried out with **1-Br**. Attempts to replace $Bi(OTf)_3$ with the less expensive analogue $BiCl_3$ gave little or no bacteriochlorin even with inclusion of various additives. Attempts to use other amines (2,6-lutidine, diisopropylethylamine, DBU, 2,3,5-collidine, imidazole, dicyclohexylmethylamine) in place of 2,6-DTBP in conjunction with TMSOTf generally failed to give any bacteriochlorin, as did use of related silicon-based species (TMSOTf/$InCl_3$, $TMSNTf_2$, and TIPSOTf/2,6-DTBP) except TMSI/2,6-DTBP, which afforded **MeOBC-Br** in 30% yield. Examination of other solvents (CH_2Cl_2, CH_3CN, toluene, CH_3NO_2, $ClCH_2CH_2Cl$) in conjunction with $Bi(OTf)_3$ or TMSOTf/2,6-DTBP gave no improvements although some of the solvents also supported formation of bacteriochlorins. These studies are described in the Supporting Information.

The formation of **TDC**-type macrocycles has only been indicated by TLC analysis (**TDC-T** has been fully characterized previously[11]), and such ring-contracted macrocycles were not separated or completely characterized. Some Lewis acids identified during the broad survey were especially efficient in forming **TDC**-type macrocycles. Tentatively assigned on the basis of TLC analysis, the efficiency appears to decrease in order of $Yb(OTf)_3 \sim Yb(NTf_2)_3 > Sc(OTf)_3 \sim Er(OTf)_3 > Dy(OTf)_3 \sim Eu(OTf)_3 > Ln(OTf)_3$.

2. Application of New Acid Catalysis Conditions. The most promising acids identified in the broad survey were applied to the self-condensation of dihydrodipyrrin-acetals **1-Br**, **1-T**, **1-H**, **1-EtEs**, **1-EtEt**, and **1-EsEs** at various concentrations of the dihydrodipyrrin-acetal and the acid. The most promising acid and solvent combinations (all in CH_2Cl_2) were as follows: $Bi(OTf)_3$, $Hf(OTf)_4$, $HfCl_4$, and TMSOTf/2,6-DTBP. In addition,

(28) (a) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, Vols. 1 and 2, 2000. (b) *Acid Catalysis in Modern Organic Synthesis*; Yamamoto, H., Ishihara, K. Eds.; Wiley-VCH:Weinheim, 2008.

(29) (a) Gaspard-Iloughmane, H.; Le Roux, C. *Eur. J. Org. Chem.* **2004**, 2517–2532. (b) Dilman, A. D.; Ioffe, S. L. *Chem. Rev.* **2003**, *103*, 733–772. (c) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227–2302.

(30) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259–4275.

TABLE 2. Self-Condensation of Dihydrodipyrrin-Acetals[a]

			bacteriochlorins (% yields)	
entry	reactant	Lewis acid	**HBC-T**	**MeOBC-T**
1	**1-T**	$Bi(OTf)_3$	3.4	25
2	**1-T**	$Hf(OTf)_4 \cdot xH_2O$	15	25
3	**1-T**	$HfCl_4$	-[c]	2.9
4	**1-T**	TMSOTf/2,6-DTBP	-[c]	32
5	**1-T**	$BF_3 \cdot O(Et)_2/CH_3CN$	27	-[c]
			bacteriochlorins (% yields)	
entry	reactant	Lewis acid	**HBC-Br**	**MeOBC-Br**
6	**1-Br**	$Bi(OTf)_3$	6.2	3.6
7	**1-Br**	$Hf(OTf)_4 \cdot xH_2O$	-[c]	-[c]
8	**1-Br**	$HfCl_4$	-[c]	-[c]
9	**1-Br**	TMSOTf/2,6-DTBP	-[c]	33
10	**1-Br**	$BF_3 \cdot O(Et)_2/CH_3CN$	13	-[c]
			bacteriochlorins (% yields)	
entry	reactant	Lewis acid	**HBC-H**	**MeOBC-H**
11	**1-H**	$Bi(OTf)_3$	7.8	9.6
12	**1-H**	$Hf(OTf)_4 \cdot xH_2O$	3.4	-[c]
13	**1-H**	$HfCl_4$	-[c]	-[c]
14	**1-H**	TMSOTf/2,6-DTBP	-[c]	21
15	**1-H**	$BF_3 \cdot O(Et)_2/CH_3CN$	1.9	-[c]
			bacteriochlorins (% yields)	
entry	reactant	Lewis acid	**HBC-EtEs**	**MeOBC-EtEs**
16	**1-EtEs**	$Bi(OTf)_3$	2.9	15
17	**1-EtEs**	$Hf(OTf)_4 \cdot xH_2O$	1.1	0.9
18	**1-EtEs**	$HfCl_4$	7.4	4.5
19	**1-EtEs**	TMSOTf/2,6-DTBP	-[c]	42
20	**1-EtEs**	$BF_3 \cdot O(Et)_2/CH_3CN$	28	-[c]
			bacteriochlorins (% yields)	
entry	reactant	Lewis acid	**HBC-EtEt**	**MeOBC-EtEt**
21	**1-EtEt**	$Bi(OTf)_3$	< 1	< 1
22	**1-EtEt**	$Hf(OTf)_4 \cdot xH_2O$	-[c]	-[c]
23	**1-EtEt**	$HfCl_4$	-[c]	-[c]
24	**1-EtEt**	TMSOTf/2,6-DTBP	-[c]	-[c]
25	**1-EtEt**	$BF_3 \cdot O(Et)_2/CH_3CN$	-[c]	-[c]
			bacteriochlorins (% yields)	
entry	reactant	Lewis acid	**HBC-EsEs**	**MeOBC-EsEs**
26	**1-EsEs**[b]	$Bi(OTf)_3$	-[c,d]	-[c,d]
27	**1-EsEs**[b]	$Hf(OTf)_4 \cdot xH_2O$	-[c,d]	-[c,d]
28	**1-EsEs**[b]	$HfCl_4$	-[c,d]	-[c,d]
29	**1-EsEs**[b]	TMSOTf/2,6-DTBP	-[c,d]	8.5[d]
30	**1-EsEs**[b]	$BF_3 \cdot O(Et)_2/CH_3CN$	-[c,d]	-[c,d]

[a]All reactions were carried out with 18 mM dihydrodipyrrin-acetal at room temperature and in CH_2Cl_2 except those with $BF_3 \cdot O(Et)_2$, which employed CH_3CN. The acid concentrations were 140 mM [$Bi(OTf)_3$, $Hf(OTf)_4 \cdot xH_2O$, $HfCl_4$, and $BF_3 \cdot O(Et)_2$] or 90 mM [TMSOTf with 360 mM 2,6-DTBP]. Each reaction was carried out for 16 h unless noted otherwise. Yields were determined by absorption spectroscopy of samples isolated by chromatography (limit of detection ~0.4%). [b]Reaction for 48 h. [c]Not detected. [d]Unreacted dihydrodipyrrin-acetal remained.

$BF_3 \cdot O(Et)_2$ in CH_3CN was used for comparison with prior data from the self-condensation of **1-T** and **1-Br**.

In our previous work,[11] the self-condensation of **1-T** using $BF_3 \cdot O(Et)_2$ in CH_3CN at nearly equimolar concentrations of **1-T** and $BF_3 \cdot O(Et)_2$ (10 and 11 mM, respectively) gave **TDC-T** as the major macrocyclic product. At concentrations of 5 mM **1-T** and 50 mM $BF_3 \cdot O(Et)_2$ the major product was **MeOBC-T**, whereas at concentrations of 18 mM **1-T** and 140 mM $BF_3 \cdot O(Et)_2$ the major product was **HBC-T**. According to these results the two concentrations chosen for the self-condensation study were 5 mM **1**/50 mM acid and 18 mM **1**/140 mM acid, except for the reactions using TMSOTf/2,6-DTBP. The latter were carried out with concentrations of **1**/TMSOTf/2,6-DTBP = 5 mM/25 mM/100 mM and 18 mM/80 mM/320 mM. In total, each of the six dihydrodipyrrin-acetals was subjected to 10 different reaction conditions.

The results from reactions of the six dihydrodipyrrin-acetals at higher concentrations (18 mM **1**) are provided in Table 2. The results at lower concentrations (5 mM **1**) are provided in the Supporting Information. A number of trends emerged from this study. First, TMSOTf/2,6-DTBP afforded the highest yield and the greatest selectivity of macrocycle formation for most of the dihydrodipyrrin-acetals. Indeed, the bacteriochlorins **MeOBC-T**, **MeOBC-Br**, **MeOBC-H**, **MeOBC-EtEs**, and **MeOBC-EsEs** were the only observed macrocycles, with no isolable amounts of the

TABLE 3. Preparative Synthesis of Bacteriochlorins[a]

reactant	scale (mmol of **1**)	product	% yield	isolated amount (mg)
1-Br[b]	0.61	**MeOBC-Br**	32	55
1-H[c]	1.7	**MeOBC-H**	44	150
1-EtEs[d]	2.1	**HBC-EtEs**	41	250
1-EtEs[b]	0.53	**MeOBC-EtEs**	40	64
1-EsEs[b,e]	0.076	**MeOBC-EsEs**	63	16.5
1-Es[b]	2.2	**MeOBC-Es**	8.4	50
1-AnEs[c]	0.33	**MeOBC-AnEs**	32	40
1-MeEs[c]	0.21	**MeOBC-MeEs**	48	29
1-ArEs[b]	0.077	**MeOBC-ArEs**	36	13

[a]All reactions were carried out at room temperature for 16 h unless noted otherwise. [b]18 mM reactant, 90 mM TMSOTf, and 360 mM 2,6-DTBP in CH_2Cl_2. [c]5 mM reactant, 25 mM TMSOTf, and 100 mM 2,6-DTBP. [d]18 mM reactant and 140 mM $BF_3 \cdot O(Et)_2$ in CH_3CN. [e]Reaction for 4 days.

corresponding **HBC**-type macrocycles. Second, the next best among the new acid conditions was $Bi(OTf)_3$, which in each case afforded a mixture of the **HBC**-type and **MeOBC**-type macrocycles. Third, the only dihydrodipyrrin-acetal that failed to afford significant quantities of bacteriochlorin was the electron-rich **1-EtEt** (used immediately upon preparation), which was observed to be quite unstable (vide supra). The reaction mixture from **1-EtEt** with catalysis by $Bi(OTf)_3$ showed absorption bands at 350, 374, 500, and 719 nm (in CH_2Cl_2) and molecule ion peaks at m/z 482.4 (**HBC-EtEt**) and 512.6 (**MeOBC-EtEt**), but the overall yield was very low. Finally, we note that the use of the original acid catalysts [$BF_3 \cdot O(Et)_2/CH_3CN$] at the specified concentrations with several dihydrodipyrrin-acetals herein tended to give exclusively the **HBC**-type macrocycle, as observed for **HBC-T**, **HBC-Br**, **HBC-H** (albeit in very low yield), and **HBC-EtEs** (Table 2). The selective formation of **HBC-Br** was observed previously,[8] but **HBC-T** and **MeOBC-T** have been obtained previously from **1-T** using $BF_3 \cdot O(Et)_2$ in 49% and 30% yield, respectively.[11]

The best conditions identified in each case were employed at a 0.076−2.2 mmol scale to obtain complete characterization and isolated (gravimetric) yields of each macrocycle. The yields obtained in the larger scale reactions generally corresponded well to those obtained in the small-scale survey reactions (Table 3). The only discrepancy was for **MeOBC-EsEs**, which was observed in 8.5% yield in the microscale study (2 day reaction) but in 63% upon scaleup (4 day reaction).

The TMSOTf/2,6-DTBP acid catalysis conditions also were applied to dihydrodipyrrin-acetals **1-Es**, **1-AnEs**, **1-MeEs**, and **1-ArEs** to give bacteriochlorins **MeOBC-Es**, **MeOBC-AnEs**, **MeOBC-MeEs**, and **MeOBC-ArEs** in 8.4%, 32%, 48%, and 36% yield, respectively (Table 3). However, the same conditions applied to **1-Py** resulted in very low yield of **MeOBC-Py** (< 1%). The low yield may stem from incompatibility of the pyridyl moiety of **1-Py** with the acid catalysis conditions for the self-condensation process. Nonetheless, the new acid catalysis conditions have afforded eight new 5-methoxybacteriochlorins in reasonable yield, in each case without noticeable accompaniment of other macrocycles.

III. Bromination of MeOBC-Type Bacteriochlorins. Previously, our group has explored the bromination of the *p*-tolyl-substituted bacteriochlorins **HBC-T** and **MeOBC-T** to obtain bacteriochlorin building blocks.[31] Bromination of **HBC-T** occurred at the β and/or meso positions to afford a mixture of mono- and dibromobacteriochlorins; by contrast, treatment of **MeOBC-T** with NBS cleanly afforded the corresponding 15-bromobacteriochlorin. The ability to selectively brominate the 15-position of **MeOBC-T** enabled the synthesis of diverse bacteriochlorins.[10,31,32] However, it was unclear whether the selective 15-bromination was unique to **MeOBC-T** and, in particular, whether the selectivity for 15-bromination of **MeOBC-T** stems solely from the electronic effect of the 5-methoxy substituent or is aided by the steric effects of the 2,12-di-*p*-tolyl substituents. The new 5-methoxybacteriochlorins obtained herein allowed further studies to probe such issues.

To investigate the electronic effect of the 5-methoxy substituent, **MeOBC-H** (lacking any β substituents) was treated with NBS (1 equiv) in THF at room temperature for 1 h. The reaction proceeded cleanly to afford a single new product upon examination by TLC analysis. While the resonances of each proton in the ^{1}H NMR spectrum were not assigned due to the overlapping chemical shifts of the meso and β protons, the disappearance of a cross peak in the NOESY-NMR stemming from the $-CH_2-$ at the 17-position and the proton at the 15-position suggested that bromination took place at the 15-position to afford **MeOBC-H-Br**[15]. For further confirmation, putative **MeOBC-H-Br**[15] was subjected to palladium coupling conditions[33] to substitute the bromine atom with a methoxy group. ^{1}H NMR spectroscopy of the resulting dimethoxybacteriochlorin gave a simplified spectrum consistent with the nominal C_{2h} symmetry of the product **BC-OMe**[5,15], thereby confirming the regioselective 15-bromination in the preceding step (Scheme 3). By contrast, treatment of unsubstituted **HBC-H** with NBS (1 equiv) in THF resulted in a mixture of at least three bromobacteriochlorins (TLC analysis), which upon LD-MS analysis showed peaks (m/z = 448.1, 526.1) consistent with mono- and dibromobacteriochlorins. Thus, given the presence of sterically unhindered meso and β-pyrrole sites, the electronic effect of the 5-methoxy group alone directs bromination preferentially to the 15-position.

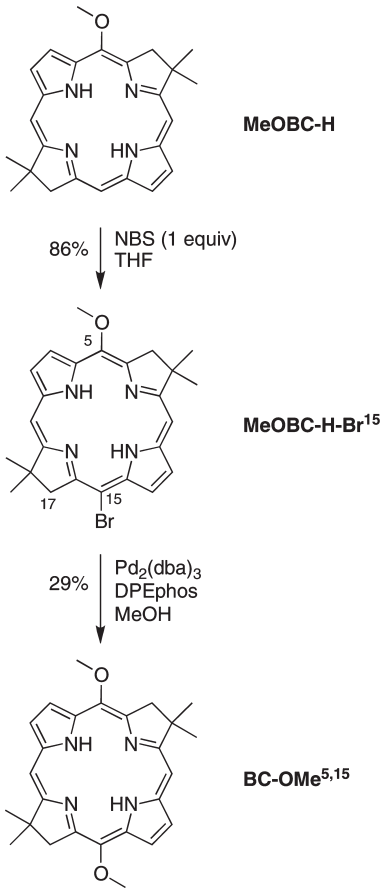
Treatment of the 5-methoxybacteriochlorin **MeOBC-Es** with NBS (1 equiv) in THF at room temperature for 1 h afforded a mixture of mono- and dibrominated bacteriochlorins. Column chromatography afforded four fractions: (i) the β-substituted bromobacteriochlorin **MeOBC-Es-Br**[12] (15%), (ii) a mixture of mono- and dibrominated bacteriochlorins (LD-MS m/z = 622.2, m/z = 700.1) that

(31) Fan, D.; Taniguchi, M.; Lindsey, J. S. *J. Org. Chem.* **2007**, *72*, 5350–5357.

(32) Muthiah, C.; Taniguchi, M.; Kim, H.-J.; Schmidt, I.; Kee, H. L.; Holten, D.; Bocian, D. F.; Lindsey, J. S. *Photochem. Photobiol.* **2007**, *83*, 1513–1528.

(33) Gao, G.-Y.; Ruppel, J. V.; Allen, D. B.; Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2007**, *72*, 9060–9066.

SCHEME 3. Regioselective 15-Bromination of MeOBC-H

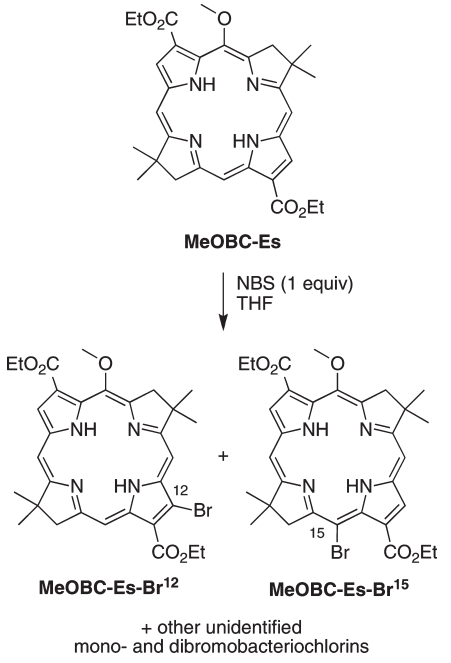


was not analyzed further, (iii) remaining starting material **MeOBC-Es** (30%), and (iv) the 15-bromobacteriochlorin **MeOBC-Es-Br^{15}** (13%) (Scheme 4). Thus, the 3,13-bis-(ethoxycarbonyl) substituents interfere with the directive influence of the 5-methoxy group.

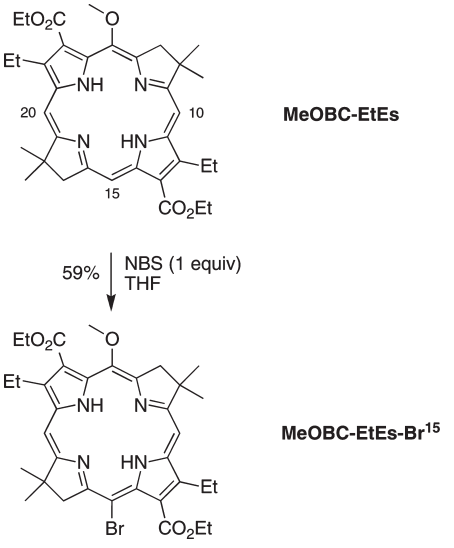
The same bromination conditions were applied to 5-methoxybacteriochlorin **MeOBC-EtEs**, which contains an ethoxycarbonyl and an ethyl group in each pyrrole and hence cannot undergo β-pyrrole bromination. In this case, the 15-bromobacteriochlorin **MeOBC-EtEs-Br^{15}** was obtained as the only isolated product in 59% yield (Scheme 5).

IV. Characterization. The bacteriochlorins were characterized by ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy (where sufficient sample permitted), high-resolution mass spectrometry (ESI-MS), and absorption spectroscopy. The bacteriochlorins for which insufficient sample was available for ^{13}C NMR spectroscopy include **MeOBC-Es**, **MeOBC-Py**, and the brominated series of bacteriochlorins. The bacteriochlorins prepared herein exhibit characteristic bacteriochlorin absorption spectra,[1] with near-UV bands and a long-wavelength band in the NIR region of comparable intensity. The long-wavelength (Q_y) absorption band appears in the spectral region of 707−759 nm (Table 4). The

SCHEME 4. Bromination of MeOBC-Es



SCHEME 5. Regioselective 15-Bromination of MeOBC-EtEs

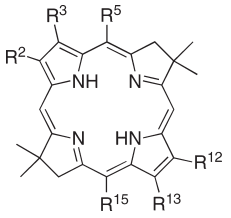


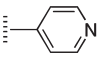
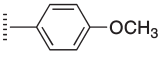
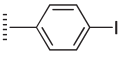
fwhm of the Q_y band was 13−24 nm. The sharpness of the bands renders the synthetic bacteriochlorins well suited for elaboration as biomedical imaging probes[34,35] or as fluorescent markers in polychromatic flow cytometry.[8] The Q_y band of the **MeOBC**-type bacteriochlorins shows a hypsochromic shift of 4−20 nm upon comparison to the **HBC**-type analogues. The position of the Q_x band also varies among the substituted bacteriochlorins. The spectra of selected bacteriochlorins in CH_2Cl_2 are shown in Figure 1. The spectra displayed include those of all available pairs of bacteriochlorins wherein the members of a pair differ only in the presence a 5-methoxy versus 5-H group. The spectrum of **MeOBC-EsEs**, the 5-methoxybacteriochlorin with the longest wavelength Q_y band among those prepared herein, also is displayed.

(34) Kee, H. L.; Nothdurft, R.; Muthiah, C.; Diers, J. R.; Fan, D.; Ptaszek, M.; Bocian, D. F.; Lindsey, J. S.; Culver, J. P.; Holten, D. *Photochem. Photobiol.* **2008**, *84*, 1061–1072.

(35) Kee, H. L.; Diers, J. R.; Ptaszek, M.; Muthiah, C.; Fan, D.; Lindsey, J. S.; Bocian, D. F.; Holten, D. *Photochem. Photobiol.* **2009**, *85*, 909–920.

TABLE 4. Long-Wavelength Absorption Band of 15 New Bacteriochlorins



Bacteriochlorin	R^2 and R^{12}	R^3 and R^{13}	R^5	R^{15}	λ_{Qy} (nm)[a]
BC-OMe[5,15]	H	H	-OMe	-OMe	707
MeOBC-H	H	H	-OMe	H	709
MeOBC-H-Br[15]	H	H	-OMe	Br	712
MeOBC-Br	H	Br	-OMe	H	722
MeOBC-EsBr[15]	H	$-CO_2Et$	-OMe	Br	724
MeOBC-EtEsBr[15]	$-CH_2CH_3$	$-CO_2Et$	-OMe	Br	726
MeOBC-Py	H		-OMe	H	734
MeOBC-Es	H	$-CO_2Et$	-OMe	H	735
MeOBC-MeEs	$-CH_3$	$-CO_2Et$	-OMe	H	738
MeOBC-EtEs	$-CH_2CH_3$	$-CO_2Et$	-OMe	H	739
MeOBC-EsBr[12]	R^2 = H, R^{12} = Br	$-CO_2Et$	-OMe	H	740
MeOBC-AnEs		$-CO_2Et$	-OMe	H	750
MeOBC-ArEs		$-CO_2Et$	-OMe	H	751
MeOBC-EsEs	$-CO_2Et$	$-CO_2Et$	-OMe	H	758
HBC-EtEs	$-CH_2CH_3$	$-CO_2Et$	H	H	759

[a]All data are in CH_2Cl_2 at room temperature.

Discussion

The development of robust access to bacteriochlorins requires new methods of synthesis as well as conditions that support the conversion of diverse precursors to this valuable class of macrocycles. The identification of mild acid catalysis conditions for the self-condensation of dihydrodipyrrin-acetals is essential for the widespread use of the de novo synthetic route. Here we first discuss the new acid catalysis conditions and the scope of bromination of intact bacteriochlorins and then consider tactics for planning synthetic routes to bacteriochlorin target molecules given the available methods for introduction of substituents into dihydrodipyrrin-acetal precursors versus derivatization of intact bacteriochlorin macrocycles.

1. Overview of Acid Conditions. The development of syntheses of tetrapyrrole macrocycles that entail acid-catalyzed condensation of pyrrolic or pyrromethane substrates has an obvious requirement for the identification of suitable acid-catalysis conditions. The search for acid-catalysis conditions in tetrapyrrole chemistry remains a largely empirical process. The acid-catalysis conditions identified

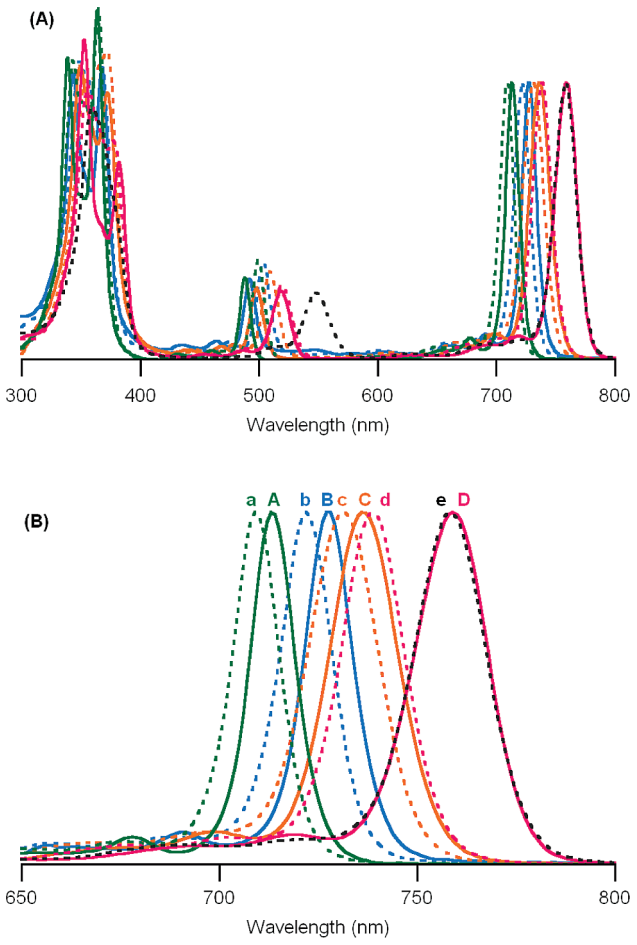


FIGURE 1. Absorption spectra in CH_2Cl_2 at room temperature of bacteriochlorins (normalized at the Q_y bands): (A) entire spectra; (B) magnification of the Q_y region. The labels and colors in the graph are as follows: **HBC**-type bacteriochlorin (—) and **MeOBC**-type bacteriochlorin (--); **MeOBC-H** (a, green), **HBC-H** (A, green), **MeOBC-Br** (b, light blue), **HBC-Br** (B, light blue), **MeOBC-T** (c, orange), **HBC-T** (C, orange), **MeOBC-EtEs** (d, magenta), **HBC-EtEs** (D, magenta), and **MeOBC-EsEs** (e, black).

through extensive searching for the synthesis of porphyrins (via aldehyde and pyrrole, aldehyde and dipyrromethanes, or dipyrromethane-carbinol condensations)[15] have subsequently been applied to the synthesis of their precursors (e.g., dipyrromethanes, bilanes)[36,37] as well as hydroporphyrin macrocycles such as chlorins[38,39] and bacteriochlorins.[11] The initial conditions developed for room-temperature porphyrin-forming reactions typically employed a relatively strong Brønsted or Lewis acid in a solvent of modest polarity (e.g., TFA or $BF_3 \cdot O(Et)_2$ in CH_2Cl_2). The migration to reactions where acidolytic scrambling of more elaborate precursors (such as dipyrromethanes) was a potential problem entailed the development of milder catalysis conditions, such as obtained with a mild Lewis acid. Examples of mild Lewis acids employed for room-temperature reaction include $InCl_3$, $Yb(OTf)_3$, $Sc(OTf)_3$, or $Dy(OTf)_3$ in CH_2Cl_2;[40] $Yb(OTf)_3$/2,6-DTBP in CH_2Cl_2;[41] $Sc(OTf)_3$/2,6-DTBP in CH_2Cl_2;[42] and $Yb(OTf)_3$ in methanolic CH_3CN.[37] Scrambling is not an issue in the reaction of a dihydrodipyrrin-acetal to form the bacteriochlorin; however, the only acid catalysis conditions used heretofore for the self-condensation of dihydrodipyrrin-acetals entailed $BF_3 \cdot O(Et)_2$ in CH_3CN,[11] which resembled the conditions employed some 10−20 years ago for porphyrin-forming reactions.[15] The mixtures of three macrocycles (**HBC**-, **MeOBC**-, and **TDC**-type macrocycles) along with the low and varying yields obtained upon application of $BF_3 \cdot O(Et)_2$ to other dihydrodipyrrin-acetals prompted exploration of conditions to achieve greater selectivity and higher yields.

The systematic survey herein of >20 different acids, different additives and solvents identified $Bi(OTf)_3$, $Hf(OTf)_4$, $HfCl_4$, and TMSOTf/2,6-DTBP in CH_2Cl_2 as the best catalysts for the self-condensation of dihydrodipyrrin-acetals to give the bacteriochlorin macrocycle. $Bi(OTf)_3$, $Hf(OTf)_4$, and $HfCl_4$ usually gave mixtures of **HBC**- and **MeOBC**-type macrocycles in low to moderate yields for the dihydrodipyrrin-acetals examined herein. $BF_3 \cdot O(Et)_2$ usually gave **HBC**-type macrocycles in low yields (<5%) with the exception of **HBC-EtEs** (41% yield). However, TMSOTf/2,6-DTBP in CH_2Cl_2 gave the **MeOBC**-type macrocycle in yields of up to 63% for the various dihydrodipyrrin-acetals, to the apparent exclusion of other macrocycles. We also note that whereas the use of $BF_3 \cdot O(Et)_2$ catalysis with **1-Br** in some instances gave a chlorin impurity,[8] we did not observe any chlorin impurities upon application of the new acid catalysis conditions to the set of dihydrodipyrrin-acetals shown in Chart 2 and Scheme 2.

The role of 2,6-DTBP is not well understood, as no reaction intermediates were isolated. The hindered base 2,6-DTBP[43] can act as a proton sponge but does not bind to bulky Lewis acids and, hence, has been employed to discriminate Lewis and Brønsted acid catalysis.[41] Lewis acids are known to promote formation of Brønsted acids in the presence of water or other XH species, thereby providing a source of protons.[44] In fact, protonation of the bacteriochlorin is observed via UV−vis spectroscopy of the crude self-condensation reaction mixtures [with $Bi(OTf)_3$, $Hf(OTf)_4$, or $HfCl_4$ in CH_2Cl_2; or $BF_3 \cdot O(Et)_2$ in CH_3CN] as evidenced by the bathochromic shift of the Q_y band [e.g., **HBC-T** shifts from 737 nm (neutral) to 796 nm (protonated)]. It is not clear to what extent the Brønsted acid plays a role in formation of the bacteriochlorin and/or distribution of macrocycles (**HBC**-, **MeOBC**-, and **TDC**-type). However, exclusive formation of **MeOBC**-type macrocycles with TMSOTf and 2,6-DTBP (which serves as a Brønsted acid scavenger) suggests that a Brønsted acid is necessary during the in situ reduction process to form

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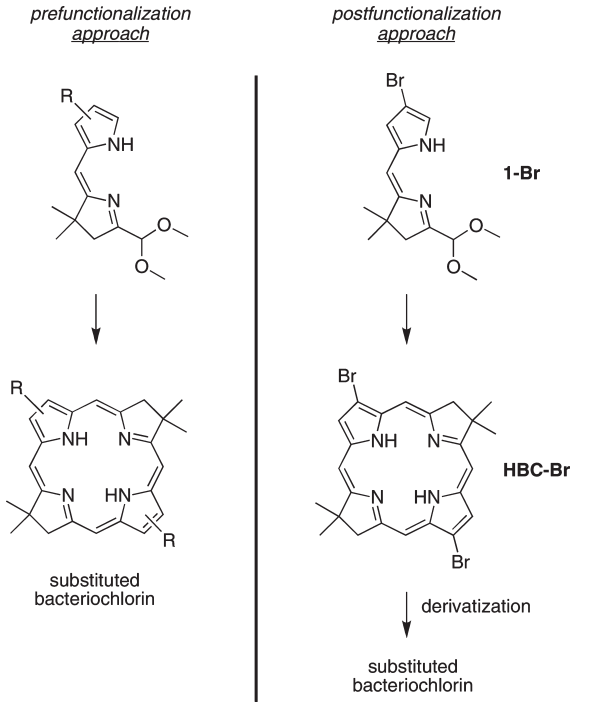
HBC-type macrocycles. TMSOTf/base combinations such as TMSOTf/2,6-lutidine have been reported to give effective deprotection of acetals via an unstable pyridinium salt.[45] However, use of 2,6-lutidine herein as an additive gave only a trace amount of bacteriochlorin (see the Supporting Information). 2,6-DTBP has been used in combination with TMSOTf for the Lewis acid catalyzed aldol-type reaction of enol silyl ethers and acetals.[30] A silylated pyridinium triflate is proposed as the actual silylating agent for the acetal substrate, generating a better leaving group to form the carboxonium triflate and thereby accomplishing the aldol reaction.[30]

2. Regioselective Bromination. TMSOTf/2,6-DTBP in CH_2Cl_2 provides generic, mild, and selective reaction conditions for the formation of **MeOBC**-type macrocycles in higher yields than previously obtained for self-condensation of dihydrodipyrrin-acetals. A further advantage of such conditions is that a number of **MeOBC**-type bacteriochlorins undergo regioselective 15-bromination, providing an avenue for derivatization of the bacteriochlorin as a molecular building block in the construction of larger architectures.[10,31,32] The bacteriochlorin lacking the 5-methoxy group (**HBC-T**), by contrast, gives a mixture of brominated bacteriochlorins.[31] Although further studies are required to explore the scope of halogenation, the 5-methoxybacteriochlorins now known to give regioselective 15-bromination include the unsubstituted parent bacteriochlorin (**MeOBC-H**), the 2,12-di-*p*-tolylbacteriochlorin (**MeOBC-T**), and a bacteriochlorin bearing substituents at all of the β-pyrrole sites (**MeOBC-EtEs**). The results with the latter bacteriochlorin may point to a general result, whereupon blocking each β-pyrrole position results in the 15-position as the least hindered of the three open sites (10, 15, 20).

3. Tactical Considerations in Synthetic Planning. The route to bacteriochlorins described herein relies on the preparation of dihydrodipyrrin-acetals and their subsequent self-condensation to form the bacteriochlorin macrocycle. Two possible routes to installing a desired functional group on the bacteriochlorin macrocycle can be envisioned: (1) a prefunctionalization approach, where the desired substituent is installed on the pyrrole precursor and carried through the dihydrodipyrrin-acetal to the bacteriochlorin, and (2) a postfunctionalization approach, where a halobacteriochlorin is derivatized with diverse groups (Scheme 6). The former route has been exploited for the synthesis of bacteriochlorins bearing *p*-tolyl,[11] mesityl,[14] or swallowtail[13] substituents, whereas the latter has been employed in the derivatization of dibromobacteriochlorin **HBC-Br** via a range of palladium coupling reactions,[8,46] as well as subsequent aldol condensations, amidations, aminoalkylations, and quaternization processes.[47]

The stability of the synthetic bacteriochlorins toward various reaction conditions (e.g., palladium coupling reactions, aldol condensations) makes the postfunctionalization route attractive and has resulted in a wide range of synthetic bacteriochlorins. However, introduction of certain substituents, such as alkyl groups, may be difficult to accomplish via functionalization of a halobacteriochlorin. The introduction

SCHEME 6. Distinct Routes for the Preparation of β-Pyrrole-Substituted Bacteriochlorins



of a desired substituent early in the synthesis avoids the palladium-coupling step used for derivatizing the halobacteriochlorin and may afford a shorter synthesis. For example, the synthesis of the bromodihydrodipyrrin-acetal (**1-Br**) requires two additional steps (protection and deprotection of the pyrrole NH),[18] while the synthesis of each of the dihydrodipyrrin-acetals described herein did not require any protective measures. The results obtained herein for a wide variety of substituted dihydrodipyrrin-acetals point out the advantages and limitations of the prefunctionalization route:

(**a**) **Pyridyl Substituent.** The dihydrodipyrrin-acetal **1-Py** (containing a pyridyl group) was synthesized to explore the possibility of preparing a pyridyl-substituted bacteriochlorin. The only known synthetic amine-substituted bacteriochlorins contain alkylamines (prepared by derivatization of **HBC-Br**,[46] Scheme 6) rather than pyridyl units. However, the difficulties in preparing **1-Py** (low solubility and low yields) along with the very low yields for formation of **MeOBC-Py** suggests that pyridyl-substituted bacteriochlorins should be prepared via derivatization of intact bacteriochlorins (e.g., **HBC-Br**).

(**b**) **One Neutral Aryl Substituent.** Dihydrodipyrrin-acetal **1-T** gave **MeOBC-T** in 32% yield, indicating the attractiveness of the prefunctionalization route.

(**c**) **One Ester Substituent.** Dihydrodipyrrin-acetal **1-Es** gave **MeOBC-Es** in only 8.4% yield; this bacteriochlorin could in principle be prepared via derivatization of the analogous dibromobacteriochlorin. In this regard, the 3,13-dibromobacteriochlorin lacking the 5-methoxy group (**HBC-Br**) was converted to the corresponding methyl ester via a palladium-mediated carbonylation process.[46]

(**d**) **One Ester and One Neutral Alkyl/Aryl Substituent.** Dihydrodipyrrin-acetal **1-EtEs** gave the resulting bacteriochlorins **HBC-EtEs** and **MeOBC-EtEs** in a straightforward

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manner with relatively good yields for each step, stable and readily purifiable intermediates, and selective reaction conditions to give the distinct macrocycles. Accordingly, up to 250 mg of bacteriochlorin (**HBC-EtEs**, **MeOBC-EtEs**) was obtained in about one week from the simple precursors (ethoxycarbonylmethylene)triphenylphosphorane and propionaldehyde. Analogous dihydrodipyrrin-acetals (**1-AnEs**, **1-MeEs**, and **1-ArEs**) gave the corresponding 5-methoxybacteriochlorins in 32%, 48%, and 36% yield, respectively. Such substituent patterns are best achieved by the prefunctionalization approach.

(e) Two Ester Substituents. The self-condensation of **1-EsEs** to give **MeOBC-EsEs** bearing four electron-withdrawing substituents proceeded in excellent yield (63% after 4 days). However, the synthesis of **1-EsEs** was rather difficult, with low yields especially for the Michael addition and the subsequent reductive cyclization. The low yields may stem from competing intermolecular cyclization between the nitronate anion and the ester substituents at the 3-position of the pyrrole. Regardless, the self-condensation conditions may be applied to other dihydrodipyrrin-acetals bearing two electron-withdrawing substituents such as a dicyanodihydrodipyrrin-acetal.

(f) No Substituent. The dihydrodipyrrin-acetal lacking any substituents (**1-H**) provides access to unsubstituted bacteriochlorins **HBC-H** and **MeOBC-H** in sizable quantities within about 5 days starting from commercially available pyrrole-2-carboxaldehyde. The unsubstituted bacteriochlorin **HBC-H**, which is a valuable benchmark compound for diverse studies, was previously synthesized by the more cumbersome Pd-mediated debromination of the dibromobacteriochlorin **HBC-Br**.[8]

(g) Two Alkyl Groups. The dihydrodipyrrin-acetal **1-EtEt** bears two electron-donating groups and was rather unstable. The attempted self-condensation of **1-EtEt** gave $<1\%$ yield of bacteriochlorin, which could stem from decomposition of **1-EtEt** before or upon treatment to the acidic self-condensation conditions. Thus, the synthesis of 2,3,12,13-tetraalkylbacteriochlorins appears very difficult via self-condensation of the corresponding dihydrodipyrrin-acetal. Alternative, postfunctionalization approaches can be envisioned by transformation of dialkylbacteriochlorins bearing derivatizable groups (dibromo, diacetyl, dicyano). Such bacteriochlorins should be available via the methods established herein.

In summary, the comparative utility of the prefunctionalization route depends on a number of factors including access to starting pyrroles, compatibility of substituents during the synthesis of the dihydrodipyrrin-acetal, and yield and cleanliness upon bacteriochlorin formation versus availability of the target bacteriochlorin via a postfunctionalization approach. The ready availability of stable bacteriochlorins bearing diverse substituents at the β-pyrrolic and meso-positions opens the door to examination of a wide variety of derivatization chemistries that have heretofore not been applied to bacteriochlorins, including novel iridium and rhodium catalysts that have found utility for the regioselective borylation of porphyrins and corrins.[48] Taken together, this study contributes to the scope of available bacteriochlorins for fundamental studies and diverse applications.

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Experimental Section

A. Refined Synthesis of Dihydrodipyrrin-Acetal 1-T.[11] Ethyl 3-(4-Methylphenyl)prop-2-enoate (7). A solution of *p*-tolualdehyde (24.0 g, 200 mmol) and (carbethoxymethylene)triphenylphosphorane (76.6 g, 220 mmol) in CH_2Cl_2 (250 mL) was refluxed for 24 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated and diluted with diethyl ether. The ether solution was washed (saturated brine), dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (3:1)] to give a colorless oil (36.8 g, 97%): ^{1}H NMR δ 1.33 (t, $J = 7.2$ Hz, 3H), 2.36 (s, 3H), 4.26 (q, $J = 7.2$ Hz, 2H), 6.39 (d, $J = 15.6$ Hz, 1H), 7.17 (d, $J = 8.0$ Hz, 2H), 7.41 (d, $J = 8.0$ Hz, 2H), 7.66 (d, $J = 15.6$ Hz, 1H); ^{13}C NMR δ 14.5, 21.6, 60.5, 117.3, 128.2, 129.8, 131.9, 140.8, 144.7, 167.3. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.72; H, 7.36.

3-(Ethoxycarbonyl)-4-(4-methylphenyl)pyrrole (6-TEs). A suspension of TosMIC (14.3 g, 73.5 mmol) and **7** in dry ether/DMSO (2:1) (150 mL) was added dropwise under argon to a suspension of NaH (4.20 g, 105 mmol) in ether (70 mL). The mixture was stirred at room temperature for 5 h. Water (200 mL) was added into the mixture. The aqueous phase was extracted twice with ethyl acetate (400 mL). The organic fraction was dried (Na_2SO_4) and concentrated to a brown solid. The brown solid was suspended in diethyl ether (50 mL). The suspension was sonicated and filtered, affording a pale yellow solid (11.3 g, 71%): mp 154−155 °C; ^{1}H NMR δ 1.25 (t, $J = 7.2$ Hz, 3H), 2.37 (s, 3H), 4.22 (q, $J = 7.2$ Hz, 2H), 6.77−6.78 (m, 1H), 7.16 (d, $J = 8.1$ Hz, 2H), 7.38 (d, $J = 8.1$ Hz, 2H), 7.49−7.50 (m, 1H), 8.38−8.54 (br, 1H); ^{13}C NMR δ 14.5, 21.4, 59.8, 114.1, 118.2, 125.3, 126.9, 128.6, 129.4, 131.9, 136.3, 165.0. Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.17; H, 6.72; N, 5.88.

3-(4-Methylphenyl)pyrrole (6-T). A mixture of **6-TEs** (10.3 g, 45.0 mmol) and ethylene glycol (100 mL) in a 250 mL round-bottom flask was bubbled with argon for 10 min, whereupon NaOH (18.0 g, 450 mmol; 40−80 mesh) was added. The flask was heated at 120 °C for 30 min, and then the temperature was raised to 160 °C. After 3 h, the reaction mixture was cooled to room temperature. Saturated brine (200 mL) was added. The aqueous mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed (silica, CH_2Cl_2) to give a pale yellow solid (6.61 g, 93%): mp 92−93 °C (lit.[11] mp 92−93 °C); ^{1}H NMR δ 2.34 (s, 3H), 6.51−6.53 (m, 1H), 6.81−6.82 (m, 1H), 7.04−7.06 (m, 1H), 7.15 (d, $J = 8.0$ Hz, 2H), 7.43 (d, $J = 8.0$ Hz, 2H), 8.16−8.30 (br, 1H); ^{13}C NMR δ 21.3, 106.7, 114.4, 118.9, 125.2, 125.4, 129.5, 133.1, 135.3. Anal. Calcd for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91. Found: C, 83.90; H, 7.10; N, 8.84.

2-Formyl-3-(4-methylphenyl)pyrrole (2-T). A solution of **6-T** (6.29 g, 40.0 mmol) in DMF (12.8 mL) and CH_2Cl_2 (300 mL) cooled to 0 °C under argon was treated dropwise with $POCl_3$ (4.40 mL, 48.0 mmol). After 1 h, the ice bath was removed. The flask was allowed to warm to room temperature with stirring for 18 h. The reaction mixture was cooled to 0 °C, whereupon 2.5 M aqueous NaOH (350 mL) was added. The mixture was extracted with CH_2Cl_2. The organic phase was washed with saturated brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed [silica, CH_2Cl_2/ethyl acetate (9:1)] to give a yellow solid. The ^{1}H NMR spectrum showed two regioisomers in 12:1 ratio. The yellow solid was dissolved in ethyl acetate. Hexanes was added to cause precipitation, and the resulting mixture [containing hexanes/ethyl acetate (3:1)] was cooled at −20 °C. The resulting yellow precipitate was isolated and proved to be a single regioisomer (4.97 g, 67%): mp 148−149 °C (lit.[11] mp 149−150 °C); ^{1}H NMR δ 2.41 (s, 3H), 6.42−6.44 (m, 1H), 7.10−7.11 (m, 1H), 7.26 (d, $J = 8.0$ Hz, 2H), 7.40 (d, $J = 8.0$ Hz, 2H), 9.40−9.55 (br, 1H), 9.64 (s, 1H);

^{13}C NMR δ 21.4, 111.7, 125.6, 128.9, 129.3, 129.7, 130.9, 137.2, 137.9, 180.0. Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.85; H, 5.94; N, 7.58.

3-(4-Methylphenyl)-2-(2-nitroethyl)pyrrole (3-T). A solution of acetic acid (2.00 mL, 35.5 mmol) in anhydrous THF (2.00 mL) under argon at 0 °C was treated with *n*-propylamine (2.72 mL, 33.0 mmol). The resulting *n*-propylammonium acetate mixture was kept at 0 °C for 10 min and then added dropwise to a solution of **2-T** (5.55 g, 30.0 mmol) and CH_3NO_2 (9.72 mL, 180 mmol) in anhydrous THF (28 mL) at 0 °C. After 30 min, the ice bath was removed, and the resulting mixture was stirred at room temperature. The color of the mixture changed from yellow to dark red during the course of the reaction. After 3 h, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic phase was dried (Na_2SO_4) and concentrated under high vacuum to give an orange-brown solid. The crude solid was dissolved in a mixed solvent of $CHCl_3$ (150 mL) and 2-propanol (48 mL), to which silica (36 g) was then added. The mixture was stirred vigorously, and $NaBH_4$ (2.27 g, 60.0 mmol) was added in one batch. After 3 h, the mixture was filtered. The filter cake was washed with CH_2Cl_2. The filtrate was concentrated and chromatographed [silica, hexanes/CH_2Cl_2 (2:1)] to afford a yellow solid (3.12 g, 45%): mp 81−82 °C (lit.[11] mp 81−82 °C); ^{1}H NMR (400 MHz) δ 2.37 (s, 3H), 3.44 (t, J = 6.6 Hz, 2H), 4.55 (t, J = 6.6 Hz, 2H), 6.28−6.29 (m, 1H), 6.73−6.75 (m, 1H), 7.18−7.26 (m, 4H), 8.21−8.38 (br, 1H); ^{13}C NMR δ 21.3, 24.3, 75.4, 109.8, 117.7, 122.1, 123.4, 128.2, 129.6, 133.4, 135.9. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.80; H, 5.94; N, 12.00.

1,1-Dimethoxy-4,4-dimethyl-6-[3-(4-methylphenyl)pyrrol-2-yl]-5-nitrohexan-2-one (5-T). A mixture of **3-T** (2.99 g, 13.0 mmol) and **4** (2.26 g, 14.3 mmol) was treated with DBU (5.83 mL, 39.0 mmol) at room temperature. The reaction mixture became dark and the temperature rose. After 16 h, the reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed [silica, hexanes/ethyl acetate (3:1)] to give a pale yellow solid (3.18 g, 63%): mp 99−100 °C (lit.[11] mp 98−100 °C); ^{1}H NMR δ 1.10 (s, 3H), 1.20 (s, 3H), 2.37 (s, 3H), 2.53, 2.71 (AB, ^2J = 18.9 Hz, 2H), 3.21 (ABX, ^3J = 2.4 Hz, ^2J = 15.4 Hz, 1H), 3.37 (ABX, ^3J = 11.7 Hz, ^2J = 15.4 Hz, 1H), 3.41 (s, 6H), 4.33 (s, 1H), 5.22 (ABX, ^3J = 2.4 Hz, ^3J = 11.7 Hz, 1H), 6.23−6.25 (m, 1H), 6.67−6.69 (m, 1H), 7.19 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 8.06−8.16 (br, 1H); ^{13}C NMR δ 21.3, 24.1, 24.3, 25.3, 36.8, 45.1, 55.2, 95.0, 104.7, 109.5, 117.7, 122.1, 123.7, 128.4, 129.4, 133.6, 135.7, 203.7. Anal. Calcd for $C_{21}H_{28}N_2O_5$: C, 64.93; H, 7.27; N, 7.21. Found: C, 65.11; H, 7.27; N, 7.08.

2,3-Dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyl-7-(4-methylphenyl)dipyrrin (1-T). Following a general procedure,[11] a solution of **5-T** (777 mg, 2.00 mmol) in anhydrous THF (20 mL) was bubbled with argon for 10. min and then treated with NaOMe (541 mg, 10.0 mmol). The mixture was stirred at room temperature for 1 h (the first flask). In the second flask, $TiCl_3$ (8.6 wt % $TiCl_3$ in 28 wt % HCl, 14.9 mL, 10. mmol) and water (80 mL) were mixed and bubbled with argon for 15 min; NH_4OAc (61.7 g, 800 mmol) was added to adjust the pH of the buffered mixture at 6.0, and then THF (6 mL) was added. The reaction mixture was bubbled with argon for 30 min. The mixture in the first flask that contained the nitronate anion of **5-T** was transferred via a cannula to the second flask. The resulting mixture was stirred at room temperature under argon. After 6 h, saturated aqueous $NaHCO_3$ (600 mL) was added into the reaction mixture. Then the mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated. The residue was passed over a short column [alumina, hexanes/ethyl acetate (3:1)] to give a light yellow solid (364 mg, 54%): mp 104−105 °C (lit.[11] mp 104−105 °C); ^{1}H NMR (400 MHz) δ 1.19 (s, 6H), 2.39 (s, 3H), 2.62 (s, 2H), 3.46 (s, 6H), 5.03 (s, 1H), 6.10 (s, 1H), 6.28−6.29 (m, 1H), 6.87−6.88 (m, 1H), 7.22 (d, J = 7.6 Hz, 2H), 7.35 (d, J = 7.6 Hz, 2H), 10.80−10.90 (br, 1H); ^{13}C NMR δ 21.4, 29.3, 40.5, 48.4, 54.8, 103.0, 106.3, 109.3, 119.2, 124.7, 126.9, 128.7, 129.4, 134.3, 135.4, 160.1, 174.2. Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.22; H, 7.78; N, 8.10.

B. Refined Synthesis of Dihydrodipyrrin-Acetal 1-H. 2-(2-Nitroethyl)pyrrole (3-H).[16,17] Following a general procedure,[18] a stirred mixture of pyrrole-2-carboxaldehyde (**2-H**, 9.51 g, 0.100 mol), potassium acetate (7.84 g, 0.0800 mol), and methylamine hydrochloride (5.38 g, 0.0800 mol) in absolute ethanol (35 mL) was treated with nitromethane (13.6 mL, 0.250 mol). The mixture was stirred for 2 h, whereupon water was added. The mixture was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and concentrated to a dark yellow solid. The crude solid material was dissolved in freshly distilled THF (450 mL), and the solution was cooled to −10 °C. The solution was treated with 90% $LiBH_4$ (2.64 g, 0.110 mol) all at once under vigorous stirring. The reaction mixture was stirred for ∼15 min at −10 °C, whereupon the reaction mixture was quenched by slowly adding a cold saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated to a yellow oil (13.5 g). The yellow oil turned brown within a few hours. The ^{1}H NMR data were consistent with those previously reported,[16] and indicated that the product was about 90% pure. The title compound was used directly in the next step without further purification.

1,1-Dimethoxy-4,4-dimethyl-5-nitro-6-(2-pyrrolyl)-2-hexanone (5-H).[17] Following a general procedure,[17] a mixture of crude **3-H** (13.5 g, 96.3 mmol) and **4** (18.2 g, 116 mmol, 1.2 equiv) was treated with DBU (43 mL, 0.29 mol). The reaction mixture was stirred at room temperature for 16 h under argon. A saturated solution of cold aqueous NH_4Cl was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Column chromatography (silica, CH_2Cl_2) afforded a pale brown solid (7.5 g, 25% from **2-H**): mp 73−75 °C (lit.[11] mp 74−75 °C); ^{1}H NMR δ 1.14 (s, 3H), 1.23 (s, 3H), 2.60, 2.72 (AB, ^2J = 18.6 Hz, 2H), 3.03 (ABX, ^3J = 2.4 Hz, ^2J = 15.6 Hz, 1H), 3.36 (ABX, ^3J = 11.8 Hz, ^2J = 15.6 Hz, 1H), 3.43 (s, 3H), 3.44 (s, 3H), 4.36 (s, 1H), 5.15 (ABX, ^3J = 2.4 Hz, ^3J = 11.8 Hz, 1H), 5.97−5.99 (m, 1H), 6.08−6.11 (m, 1H), 6.65−6.67 (m, 1H), 8.00−8.13 (brs, 1H); ESI-MS obsd 299.1603, calcd 299.1601 [$(M + H)^+$, $M = C_{14}H_{22}N_2O_5$]. Anal. Calcd for $C_{14}H_{22}N_2O_5$: C, 56.36; H, 7.43; N, 9.39. Found: C, 56.62; H, 7.55; N, 9.53.

2,3-Dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyldipyrrin (1-H).[17] Following a general procedure,[18] in a first flask, a solution of **5-H** (2.02 g, 6.90 mmol) in freshly distilled THF (16 mL) and anhydrous MeOH (1.0 mL) at 0 °C was treated with NaOMe (1.11 g, 20.7 mmol). The mixture was stirred and degassed by bubbling argon through the solution for 45 min. In a second flask purged with argon, $TiCl_3$ (34.7 mL, 20 wt % in 3% HCl solution, 55 mmol), 70 mL of THF, and NH_4OAc (35.1 g, 460 mmol) were combined under argon, and the mixture was degassed by bubbling argon for 45 min. Then, the first flask mixture was transferred via cannula to the buffered $TiCl_3$ mixture. The resulting mixture was stirred at room temperature for 16 h under argon. The reaction mixture was then poured over a pad of Celite and eluted with ethyl acetate. The eluant was washed with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography (neutral alumina, CH_2Cl_2) afforded a yellow oil (482 mg, 29%), which darkened within a few minutes: ^{1}H NMR δ 1.21 (s, 6H), 2.61 (s, 2H), 3.45 (s, 6H), 5.02 (s, 1H), 5.88 (s, 1H), 6.15−6.18 (m, 2H), 6.83−6.86 (m, 1H), 10.59−10.70 (brs, 1H); ^{13}C NMR δ 29.3, 40.2, 48.3, 54.8, 103.0, 107.7, 108.7, 109.4, 119.6, 130.9, 159.5, 174.1; ESI-MS obsd 249.15978, calcd 249.16030 [$(M + H)^+$, $M = C_{14}H_{20}N_2O_2$].

C. Synthesis of Dihydrodipyrrin-Acetal 1-EtEs. 3-(Ethoxycarbonyl)-4-ethylpyrrole (6-EtEs). Following a known procedure for a homologue,[25] a solution of (ethoxycarbonylmethylene)triphenylphosphorane (34.8 g, 0.100 mol) in benzene (100 mL) was treated with propionaldehyde (6.8 mL, 0.090 mol). The reaction mixture was refluxed for 2 h and then concentrated to dryness. Diethyl ether was added to the resulting white solid, and the white solid was removed by filtration using a Büchner funnel. The filtrate was concentrated, resulting in the α,β-unsaturated ester as a colorless sweet-smelling oil (crude 10. g, 87%), which was directly used in the next step. Following the van Leusen method,[26] the crude α,β-unsaturated ester (8.13 g, 63.4 mmol) and TosMIC (12.6 g, 63.4 mmol) in diethyl ether/DMSO (300 mL, 2:1) were slowly added via an addition funnel to a suspension of NaH (5.0 g, 60% in oil suspension, 0.12 mol) in 100 mL of diethyl ether. The resulting exotherm caused the mixture to reflux. The reaction was stirred at room temperature for 16 h. Water was added carefully, and the mixture was extracted with diethyl ether. The organic layer was concentrated and dried (Na_2SO_4). Column chromatography (silica, CH_2Cl_2) afforded the title compound as an oil (7.5 g, 71% from the crude α,β-unsaturated ester): ^{1}H NMR δ 1.21 (t, J = 7.4 Hz, 3 H), 1.33 (t, J = 7.2 Hz, 3 H), 2.76 (q, J = 7.4, 1.10 Hz, 2 H), 4.27 (q, J = 7.2 Hz, 2 H), 6.54 (t, J = 1.8 Hz, 1 H), 7.38 (d, J = 3.0 Hz, 1 H), 8.57 (brs, 1 H); ^{13}C NMR δ 14.8, 19.7, 59.6, 114.4, 116.3, 124.8, 128.29, 149.9, 165.8; ESI-MS obsd 168.1019, calcd 168.1019 [$(M + H)^+$, M = $C_9H_{13}NO_2$].

4-(Ethoxycarbonyl)-2-formyl-3-ethylpyrrole (2-EtEs). The Vilsmeier reagent was prepared by treatment of dry DMF (30 mL) with $POCl_3$ (4.6 mL, 49 mmol) at 0 °C and stirring of the resulting mixture for 10 min. In a separate flask, a solution of **6-EtEs** (7.5 g, 45 mmol) in DMF (150 mL) was treated with the freshly prepared Vilsmeier reagent at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and then 2 h at room temperature. The reaction mixture was treated with a mixture of saturated aqueous sodium acetate/CH_2Cl_2 [400 mL, 1:1 (v/v)] and stirred for 1 h. The water phase was separated and extracted with CH_2Cl_2. The combined organic phase was washed with a saturated LiCl solution, dried (Na_2SO_4), and concentrated. The resulting solid was dissolved in warm EtOH (~50 mL) and cooled to −15 °C. The resulting solid was filtered, washed with a small amount of cold EtOH, and dried to afford a light brown solid (6.5 g, 75%): mp 84−86 °C; ^{1}H NMR δ 1.28 (t, J = 7.4 Hz, 3H), 1.36 (t, J = 7.2 Hz, 3H), 3.08 (q, J = 7.4 Hz, 2H), 4.31 (q, J = 7.2 Hz, 2H), 7.60 (d, J = 3.3 Hz, 1H), 9.42 (brs, 1H), 9.71 (s, 1H); ^{13}C NMR δ 14.6, 17.2, 17.8, 60.2, 116.7, 131.0, 141.2, 164.1, 178.7, 202.3; ESI-MS obsd 196.0971, calcd 196.0968 [$(M + H)^+$, M = $C_{10}H_{13}NO_3$]. Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.60; H, 6.86; N, 7.12.

4-(Ethoxycarbonyl)-3-ethyl-2-(2-nitroethyl)pyrrole (3-EtEs). Following a general procedure,[18] a stirred mixture of **2-EtEs** (8.7 g, 44 mmol), potassium acetate (3.5 g, 36 mmol), and methylamine hydrochloride (2.4 g, 36 mmol) in absolute ethanol (16 mL) was treated with nitromethane (6.0 mL, 0.11 mol). The mixture was stirred for 2 h, whereupon water was added. The reaction mixture was filtered, and the filtered material was washed with water and a small amount of cold ethanol. The filtered material was dried under high vacuum to afford a yellow solid, which was used directly in the next step. The crude solid material was dissolved in $CHCl_3$/2-propanol (3:1, 346 mL). Silica (34 g) and $NaBH_4$ (2.2 g, 58 mmol) were added, and the mixture was stirred at room temperature under argon for 2 h. The reaction mixture was filtered, and the filtrate was concentrated. The resulting crude was dissolved in CH_2Cl_2. The organic solution was washed (water, brine), dried (Na_2SO_4), and concentrated to afford a pale brown solid (5.2 g, 48%): mp 95−97 °C; ^{1}H NMR δ 1.14 (t, J = 7.4 Hz, 3 H), 1.33 (t, J = 7.2 Hz, 3 H), 2.68 (q, J = 7.4 Hz, 2 H), 3.25 (t, J = 6.5 Hz, 2 H), 4.26 (q, J = 7.2 Hz, 2 H), 4.54 (t, J = 6.5 Hz, 2 H), 7.31 (d, J = 3.3 Hz, 1 H), 8.42 (brs, 1 H); ^{13}C NMR δ 14.6, 16.5, 18.2, 23.5, 59.7, 75.5, 114.8, 123.4, 124.3, 125.1, 165.5; ESI-MS obsd 241.1181, calcd 241.1183 [$(M + H)^+$, M = $C_{11}H_{16}N_2O_4$].

6-(4-(Ethoxycarbonyl)-3-ethylpyrrol-2-yl)-1,1-dimethoxy-4,4-dimethyl-5-nitrohexan-2-one (5-EtEs). Following a general procedure,[17] a mixture of **3-EtEs** (5.1 g, 21 mmol) and **4** (4.0 g, 25 mmol, 1.2 equiv) was treated with DBU (10 mL, 64 mmol). The reaction mixture was stirred at room temperature for 16 h under argon. A saturated solution of cold aqueous NH_4Cl was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Column chromatography [silica, CH_2Cl_2/ethyl acetate (9:1)] afforded a pale brown solid (3.2 g, 38%): mp 107−110 °C; ^{1}H NMR δ 1.15 (t, 3 H), 1.15 (s, 3 H), 1.25 (s, 3 H), 1.32 (t, J = 7.2 Hz, 3 H), 2.46−2.81 (m, 4 H), 3.02 (d, J = 2.2 Hz, 1 H), 3.27 (m, 1 H), 3.43 (s, 3 H), 3.44 (s, 3 H), 4.25 (q, J = 7.3 Hz, 2 H), 4.36 (s, 1 H), 5.13 (dd, J = 11.7, 2.20 Hz, 1 H), 7.27 (d, J = 1.8 Hz, 1 H), 8.26 (brs, 1 H); ^{13}C NMR δ 14.6, 16.2, 18.2, 24.48, 24.51, 24.6, 36.7, 45.3, 55.48, 55.51, 59.5, 94.8, 105.0, 114.8, 123.3, 124.1, 125.2, 165.2, 203.9; ESI-MS obsd 399.2123, calcd 399.2126 [$(M + H)^+$, M = $C_{19}H_{30}N_2O_7$]. Anal. Calcd for $C_{19}H_{30}N_2O_7$: C, 57.27; H, 7.59; N, 7.03. Found: C, 57.18; H, 7.52; N, 6.98.

8-(Ethoxycarbonyl)-2,3-dihydro-1-(1,1-dimethoxymethyl)-7-ethyl-3,3-dimethyldipyrrin (1-EtEs). Following a general procedure,[18] in a first flask, a solution of **5-EtEs** (3.2 g, 8.0 mmol) in freshly distilled THF (16 mL) and anhydrous MeOH (1.0 mL) at 0 °C was treated with NaOMe (1.3 g, 24 mmol). The mixture was stirred and degassed by bubbling argon through the solution for 45 min. In a second flask purged with argon, $TiCl_3$ (32 mL, 20 wt % in 3% HCl solution, 51 mmol), 80 mL of THF, and NH_4OAc (32 g, 418 mmol) were combined under argon, and the mixture was degassed by bubbling argon for 45 min. Then, the first flask mixture was transferred via cannula to the buffered $TiCl_3$ mixture. The resulting mixture was stirred at room temperature for 16 h under argon. The reaction mixture was then poured over a pad of Celite and eluted with ethyl acetate. The eluant was washed with a saturated aqueous solution of $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography (silica, CH_2Cl_2) afforded a yellow oil (1.3 g, 46%): ^{1}H NMR δ 1.17 (t, J = 7.4 Hz, 3H), 1.23 (s, 6H), 1.34 (t, J = 7.2 Hz, 3H), 2.63 (s, 2H), 2.82 (q, J = 7.4 Hz, 2H), 3.45 (s, 6H), 4.27 (q, J = 7.2 Hz, 2H), 5.02 (s, 1H), 5.86 (s, 1H), 7.42 (d, J = 3.0 Hz, 1H), 10.82 (brs, 1H); ^{13}C NMR δ 14.7, 16.6, 18.2, 29.4, 40.5, 48.5, 54.8, 59.4, 102.8, 104.6, 114.3, 125.3, 126.4, 128.3, 160.2, 165.6, 174.8, 202.2; ESI-MS obsd 349.2123, calcd 349.2122 [$(M + H)^+$, M = $C_{19}H_{28}N_2O_4$].

D. Synthesis of Dihydrodipyrrin-Acetal 1-EtEt. 3,4-Diethyl-2-formylpyrrole (2-EtEt). The Vilsmeier reagent was prepared by treatment of dry DMF (34 mL) by $POCl_3$ (4.6 mL, 49 mmol) at 0 °C and stirring of the resulting mixture for 10 min. In a separate flask, a solution of 3,4-diethylpyrrole (**6-EtEt**, 5.0 g, 41 mmol) in DMF (130 mL) was treated with the freshly prepared Vilsmeier reagent at 0 °C. The reaction mixture was stirred at room temperature for 2 h under argon. A saturated solution of cold aqueous NaOAc was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Column chromatography (silica, CH_2Cl_2) afforded a pale brown solid (3.3 g, 54%): mp 42−45 °C; ^{1}H NMR δ 1.20 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H), 2.46 (q, J = 7.2 Hz, 2H), 2.73 (q, J = 7.2 Hz, 2H), 6.88−6.92 (m, 1H), 9.58 (s, 1H), 9.95 (brs, 1H); ^{13}C NMR δ 14.9, 17.2, 17.3, 17.9, 124.4, 127.4, 129.1, 137.5, 177.7; ESI-MS obsd 152.1069, calcd 152.1070 [$(M + H)^+$, M = $C_9H_{13}NO$].

3,4-Diethyl-2-(2-nitroethyl)pyrrole (3-EtEt). Following a general procedure,[18] a stirred mixture of **2-EtEt** (3.3 g, 22 mmol), potassium acetate (1.7 g, 17 mmol), and methylamine hydrochloride (1.2 g, 17 mmol) in absolute ethanol (8.0 mL) was treated with nitromethane (3.0 mL, 55 mmol). The mixture was stirred for 2 h, whereupon water was added. The mixture was

extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and concentrated to a dark red solid. The crude solid material was dissolved in freshly distilled THF (40 mL), and the solution was cooled to −10 °C. The solution was treated with 90% $LiBH_4$ (0.20 g, 8.7 mmol) all at once under vigorous stirring. The reaction mixture was stirred for ∼30 min at 0 °C, whereupon the reaction mixture was quenched by slowly adding a cold saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated to a yellow oil (2.1 g, 49%). The yellow oil turned brown within a few minutes. The ^{1}H NMR data indicated that the product was about 90% pure. The title compound was used directly in the next step, without further purification, due to its limited stability.

6-(3,4-Diethylpyrrol-2-yl)-1,1-dimethoxy-4,4-dimethyl-5-nitrohexan-2-one (5-EtEt). Following a general procedure,[17] a mixture of **3-EtEt** (14.1 g, 72.2 mmol) and **4** (13.7 g, 86.6 mmol, 1.2 equiv) was treated with DBU (21.6 mL, 142 mmol). The reaction mixture was stirred at room temperature for 5 h under argon. A saturated solution of cold aqueous NH_4Cl was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Column chromatography [silica, CH_2Cl_2] afforded a yellow oil (8.7 g, 34%): ^{1}H NMR δ 1.10 (t, J = 7.6 Hz, 3H), 1.14 (s, 3H), 1.16 (t, J = 7.6 Hz, 3H), 1.25 (s, 3H), 2.34−2.44 (m, 4H), 2.65 (AB, ^2J = 18.8 Hz, 2H), 3.00 (ABX, ^3J = 2.8 Hz, ^2J = 12.8 Hz, 1H), 3.26 (ABX, ^3J = 11.6 Hz, ^2J = 13.4 Hz, 1H), 3.42 (s, 3H), 3.43 (s, 3H), 4.36 (s, 1H), 5.12 (ABX, ^3J = 2.4 Hz, ^3J = 9.2 Hz, 1H), 6.37 (m, 1H), 7.52−7.83 (brs, 1H); ^{13}C NMR δ 14.6, 16.2, 17.6, 18.6, 24.4, 24.5, 25.0, 36.7, 45.3, 55.4, 95.1, 104.9, 113.8, 121.7, 121.8 125.1, 203.8; ESI-MS obsd 355.2234, calcd 355.2227 [(M + H)$^+$, M = $C_{18}H_{30}N_2O_5$].

7,8-Diethyl-2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyldipyrrin (1-EtEt). Following a general procedure,[18] in a first flask, a solution of **5-EtEt** (8.5 g, 24 mmol) in freshly distilled THF (60 mL) and anhydrous MeOH (2 mL) at 0 °C was treated with NaOMe (3.9 g, 72 mmol). The mixture was stirred and degassed by bubbling argon through the solution for 45 min. In a second flask purged with argon, $TiCl_3$ (131 mL, 20 wt % in 3% HCl solution, 210 mmol), 245 mL of THF, and NH_4OAc (102 g, 1.32 mol) were combined under argon, and the mixture was degassed by bubbling argon for 45 min. Then the first flask mixture was transferred via cannula to the buffered $TiCl_3$ mixture. The resulting mixture was stirred at room temperature for 16 h under argon. The reaction mixture was then poured over a pad of Celite and eluted with ethyl acetate. The eluant was washed with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography [neutral alumina, CH_2Cl_2/hexanes (1:1)] afforded a yellow oil (560 mg, 7.6%): ^{1}H NMR δ 1.04−1.24 (m, 6H), 1.20 (s, 6H), 2.30−2.57 (m, 4H), 2.59 (s, 2H), 3.41 (s, 6H), 4.99 (s, 1H), 5.86 (s, 1H), 6.58 (s, 1H), 10.32 (brs, 1H). The limited stability of this compound thwarted ^{13}C NMR spectroscopy and mass spectrometric analysis.

E. Synthesis of Dihydrodipyrrin-Acetal 1-EsEs. 3,4-Bis(ethoxycarbonyl)-2-formylpyrrole (2-EsEs). The Vilsmeier reagent was prepared by treatment of dry DMF (30 mL) with $POCl_3$ (2.8 mL, 30 mmol) at 0 °C and stirring of the resulting mixture for 10 min. In a separate flask, a solution of diethyl 3,4-pyrroledicarboxylate (**6-EsEs**, 5.0 g, 24 mmol) in DMF (80 mL) was treated with the freshly prepared Vilsmeier reagent at 0 °C. The resulting mixture was heated to 80 °C in an oil bath and stirred under argon for 24 h. The reaction mixture was treated with a mixture of saturated aqueous sodium acetate/CH_2Cl_2 [300 mL, 1:1 (v/v)] and stirred for 1 h at room temperature. The water phase was separated and extracted with CH_2Cl_2. The combined organic phase was washed with saturated aqueous LiCl, dried (Na_2SO_4), and concentrated. Column chromatography [silica, hexanes/ethyl acetate (1:1)] afforded a light brown solid (3.6 g, 64%): mp 62−64 °C; ^{1}H NMR δ 1.35 (t, J = 7.2 Hz, 3H), 1.40 (t, J = 7.2 Hz, 3 H), 4.32 (q, J = 7.2 Hz, 2H), 4.43 (q, J = 7.2 Hz, 2H), 7.60 (d, J = 2.2 Hz, 1H), 9.90 (s, 1H), 10.41 (brs, 1H); ^{13}C NMR δ 14.4, 14.5, 61.1, 62.0, 118.6, 124.5, 128.9, 132.7, 162.9, 163.4, 181.2; ESI-MS obsd 240.0862, calcd 240.0866 [(M + H)$^+$, M = $C_{11}H_{13}NO_5$]. Anal. Calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.86. Found: C, 55.47; H, 5.43; N, 5.81.

3,4-Bis(ethoxycarbonyl)-2-(2-nitroethyl)pyrrole (3-EsEs). A stirred mixture of **2-EsEs** (3.5 g, 15 mmol), potassium acetate (1.2 g, 12 mmol), and methylamine hydrochloride (0.80 g, 12 mmol) in absolute ethanol (6.0 mL) was treated with nitromethane (2.0 mL, 37 mmol). The mixture was stirred for 4 h, whereupon water was added. The reaction mixture was filtered, and the filtered material was washed with water, followed by water/ethanol (1:1). The filtered material was dried under high vacuum to afford a yellow solid, which was used directly in the next step. The crude solid material (3.1 g, 11 mmol) was dissolved in $CHCl_3$/2-propanol (3:1, 133 mL). Silica (13 g) and $NaBH_4$ (0.50 g, 13 mmol) were added, and the mixture was stirred at room temperature under argon for 30 min. The reaction mixture was filtered, and the filtrate was concentrated to give a solid residue. The latter residue was dissolved in CH_2Cl_2, washed (water, brine), dried (Na_2SO_4), and concentrated. Column chromatography [silica, CH_2Cl_2/ethyl acetate (9:1)] afforded a white solid (2.5 g, 60%): mp 160−163 °C; ^{1}H NMR δ 1.34 (m, 6H), 3.48 (t, J = 6.3 Hz, 2H), 4.29 (m, 4H), 4.71 (t, J = 6.3 Hz, 2H), 7.21 (d, J = 3.0 Hz, 1H), 8.96 (brs, 1H); ^{13}C NMR δ 14.45, 14.52, 25.0, 60.7, 60.8, 74.8, 113.5, 117.4, 123.5, 133.8, 164.2, 164.8; ESI-MS obsd 285.1081, calcd 285.1081 [(M + H)$^+$, M = $C_{12}H_{16}N_2O_6$]. Anal. Calcd for $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67; N, 9.85. Found: C, 50.90; H, 5.57; N, 9.68.

6-(3,4-Bis(ethoxycarbonyl)pyrrol-2-yl)-1,1-dimethoxy-4,4-dimethyl-5-nitrohexan-2-one (5-EsEs). Following a general procedure,[17] a mixture of **3-EsEs** (1.76 g, 6.20 mmol) and **4** (9.8 g, 62 mmol, 10 equiv) was treated with DBU (2.80 mL, 18.6 mmol). The reaction mixture was stirred at room temperature for 15 min under argon. A saturated solution of cold aqueous NH_4Cl was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Column chromatography [silica, CH_2Cl_2/ethyl acetate (9:1)] afforded a yellow oil (0.56 g, 20%): ^{1}H NMR δ 1.16 (s, 3H), 1.21−1.44 (m, 6H), 1.59 (s, 3H), 2.68 (m, 2H), 3.25−3.38 (m, 1H), 3.42 (s, 3H), 3.44 (s, 3H), 3.52−3.62 (m, 1H), 4.20−4.37 (m, 4H), 4.39 (s, 1H), 5.12−5.30 (m, 1H), 7.14 (d, J = 2.9 Hz, 1H), 8.83 (brs, 1H); ^{13}C NMR δ 14.5, 23.9, 24.2, 25.2, 26.2, 36.8, 45.0, 56.0, 60.7, 74.4, 94.5, 104.7, 113.5, 117.1, 124.1, 129.7, 133.5, 164.4, 164.8, 203.6; ESI-MS obsd 465.1845, calcd 465.1844 [(M + Na)$^+$, M = $C_{20}H_{30}N_2O_9$].

7,8-Bis(ethoxycarbonyl)-2,3-dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyldipyrrin (1-EsEs). Following a general procedure,[18] in a first flask, a solution of **5-EsEs** (0.56 g, 1.3 mmol) in freshly distilled THF (3.0 mL) and anhydrous MeOH (0.5 mL) at 0 °C was treated with NaOMe (0.18 g, 3.8 mmol). The mixture was stirred and degassed by bubbling argon through the solution for 45 min. In a second flask purged with argon, $TiCl_3$ (6.4 mL, 20 wt % in 3% HCl solution, 10. mmol), 13 mL of THF, and NH_4OAc (6.5 g, 84 mmol) were combined under argon, and the mixture was degassed by bubbling argon for 45 min. Then the first flask mixture was transferred via cannula to the buffered $TiCl_3$ mixture. The resulting mixture was stirred at room temperature for 16 h under argon. The reaction mixture was then poured over a pad of Celite and eluted with ethyl acetate. The eluant was washed with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography (silica, CH_2Cl_2) afforded a yellow oil (80 mg, 16%): ^{1}H NMR δ 1.24 (s, 6H), 1.33 (t, J = 6.5 Hz, 3H), 1.37 (t, J = 6.6 Hz, 3H), 2.65 (s, 2H), 3.45 (s, 6H), 4.28 (q, J = 7.2 Hz, 2H), 4.34 (q, J = 7.2 Hz, 2H), 5.04 (s, 1H), 6.50 (s, 1H), 7.32 (d,

J = 2.8 Hz, 1H), 11.36 (brs, 1H); ^{13}C NMR δ 14.5, 14.6, 29.1, 40.8, 48.7, 54.8, 60.3, 60.5, 102.5, 105.1, 112.9, 116.6, 124.8, 135.3, 149.9, 164.6, 164.8, 165.3, 177.9, 202.2; ESI-MS obsd 393.2022, calcd 393.2020 [(M + H)$^+$, M = $C_{20}H_{28}N_2O_6$].

F. Synthesis of Dihydrodipyrrin-Acetal 1-Es. 3-Ethoxycarbonylpyrrole (6-Es). Following the van Leusen method,[26] ethyl acrylate (7.2 g, 66 mmol) and TosMIC (12.8 g, 65.6 mmol) in diethyl ether/DMSO (300 mL, 2:1) were slowly added via an addition funnel to a suspension of NaH (5.3 g, 60% in oil suspension, 0.13 mol) in 100 mL of diethyl ether. The mixture started to reflux due to the exothermic reaction. The reaction was stirred at room temperature for 3 h. Water was added carefully, and the mixture was extracted with diethyl ether (3 × 50 mL). The combined organic layer was concentrated and dried (Na_2SO_4). Column chromatography [silica, ethyl acetate/hexanes (1:3)] afforded a colorless oil (5.12 g, 56%): ^{1}H NMR δ 1.33 (t, J = 7.2 Hz, 3H), 4.27 (q, J = 7.2 Hz, 2H), 6.59−6.65 (m, 1H), 6.70−6.76 (m, 1H), 7.34−7.48 (m, 1H), 9.61 (brs, 1H); ^{13}C NMR δ 14.6, 60.1, 109.9, 116.7, 119.0, 123.7, 202.1; ESI-MS obsd 140.0708, calcd 140.0706 [(M + H)$^+$, M = $C_7H_7NO_2$]. In some cases a minor reaction product also was isolated (~8%) that is tentatively assigned to the Michael addition of the pyrrole and ethyl acrylate: ^{1}H NMR δ 1.26 (t, J = 7.2 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H), 2.63 (t, J = 6.6 Hz, 2H), 2.87 (t, J = 6.6 Hz, 2H), 4.16 (q, J = 7.2 Hz, 2H), 4.26 (q, J = 7.2 Hz, 2H), 6.32−6.34 (m, 1H), 7.28−7.30 (m, 1H), 9.04−9.19 (brs, 1H).

4-Ethoxycarbonyl-2-formylpyrrole (2-Es). The Vilsmeier reagent was prepared by treatment of dry DMF (20 mL) with $POCl_3$ (3.6 mL, 38 mmol) at 0 °C and stirring of the resulting mixture for 10 min. In a separate flask, a solution of **2-Es** (4.81 g, 34.6 mmol) in DMF (120 mL) was treated with the freshly prepared Vilsmeier reagent at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and then 15 h at room temperature. The reaction mixture was treated with a mixture of saturated aqueous sodium acetate/CH_2Cl_2 [400 mL, 1:1 (v/v)] and stirred for 1 h. The water phase was separated and extracted with CH_2Cl_2. The combined organic phase was washed with saturated aqueous LiCl, dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (1:1)] to afford a white solid (3.8 g, 65%): mp 84−85 °C; ^{1}H NMR δ 1.37 (t, J = 7.2 Hz, 3H), 4.33 (q, J = 7.2 Hz, 2H), 77.42 (s, 1H), 7.73−7.75 (m, 1H), 9.56 (s, 1H), 10.60 (brs, 1H); ^{13}C NMR δ 14.6, 60.6, 119.3, 122.0, 130.3, 133.2, 163.9, 180.3; ESI-MS obsd 168.0659, calcd 168.0655 [(M + H)$^+$, M = $C_8H_9NO_3$].

4-(Ethoxycarbonyl)-2-(2-nitroethyl)pyrrole (3-Es). A stirred mixture of **2-Es** (3.7 g, 22 mmol), potassium acetate (1.7 g, 18 mmol), and methylamine hydrochloride (1.2 g, 18 mmol) in absolute ethanol (8 mL) was treated with nitromethane (3.0 mL, 55 mmol). The mixture was stirred for 2 h, whereupon water was added. The reaction mixture was filtered, and the filtered material was washed with water and a small amount of cold ethanol. The filtered material was dried under high vacuum to afford a yellow solid, which was used directly in the next step. The crude solid material was dissolved in $CHCl_3$/2-propanol (3:1, 250 mL). Silica (24 g) and $NaBH_4$ (1.5 g, 40 mmol) were added, and the mixture was stirred at room temperature under argon for 1 h. The reaction mixture was filtered, and the filtrate was concentrated. The crude reaction mixture was dissolved in CH_2Cl_2, washed (water, brine), dried (Na_2SO_4) and concentrated to afford a pale brown solid (2.25 g, 48%): mp 118−119 °C; ^{1}H NMR δ 1.33 (t, J = 7.2 Hz, 3H), 3.29 (t, J = 6.4 Hz, 2H), 4.27 (q, J = 7.2 Hz, 2H), 4.61 (t, J = 6.4 Hz, 2H), 6.37−6.46 (m, 1H), 7.30−7.37 (m, 1H), 8.81 (brs, 1H); ^{13}C NMR δ 14.6, 25.3, 60.1, 75.1, 108.4, 117.2, 123.8, 127.5, 165.1; ESI-MS obsd 213.0873, calcd 213.0870 [(M + H)$^+$, M = $C_9H_{12}N_2O_3$]. Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 51.14; H, 5.83; N, 12.99.

6-[4-(Ethoxycarbonyl)pyrrol-2-yl]-1,1-dimethoxy-4,4-dimethyl-5-nitro-2-hexanone (5-Es). Following a general procedure,[17] a mixture of **3-Es** (2.13 g, 10.0 mmol) and **4** (4.69 g, 30.0 mmol, 3 equiv) was treated with DBU (4.7 mL, 30 mmol). The reaction mixture was stirred at room temperature for 1 h under argon. A saturated solution of cold aqueous NH_4Cl was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Column chromatography [silica, ethyl acetate/hexanes (1:1)] afforded a light brown oil (2.44 g, 66%): ^{1}H NMR δ 1.13 (s, 3H), 1.21 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H), 2.60, 2.72 (AB, ^2J = 18.6 Hz, 2H), 3.02 (ABX, ^3J = 2.2 Hz, ^2J = 15.2 Hz, 1H), 3.33 (ABX, ^3J = 12.0 Hz, ^2J = 15.2 Hz, 1H), 3.42 (s, 3H), 3.43 (s, 3H), 4.25 (q, J = 7.2 Hz, 2H), 4.37 (s, 1H), 5.16 (ABX, ^3J = 2.2 Hz, ^3J = 12.0 Hz, 1H), 6.38−6.41 (m, 1H), 7.27−7.30 (m, 1H), 8.79 (brs, 1H); ^{13}C NMR δ 14.6, 24.38, 24.46, 26.6, 36.6, 45.2, 55.3, 59.9, 94.5, 104.8, 108.5, 116.9, 123.8, 127.5, 165.2, 203.9; ESI-MS obsd 393.1642, calcd 393.1632 [(M + H)$^+$, M = $C_{17}H_{26}N_2O_7$].

8-(Ethoxycarbonyl)-1-(1,1-dimethoxymethyl)-3,3-dimethyl-2,3-dihydrodipyrrin (1-Es). Following a general procedure,[18] in a first flask, a solution of **5-Es** (2.30 g, 6.21 mmol) in freshly distilled THF (13 mL) and anhydrous MeOH (1.0 mL) at 0 °C was treated with NaOMe (540 mg, 19.8 mmol). The mixture was stirred and degassed by bubbling argon through the solution for 45 min. In a second flask purged with argon, $TiCl_3$ (34.3 mL, 20 wt % in 3% HCl solution, 54 mmol), 73 mL of THF, and NH_4OAc (26 g, 340 mmol) were combined under argon, and the mixture was degassed by bubbling argon for 45 min. Then, the first flask mixture was transferred via cannula to the buffered $TiCl_3$ mixture. The resulting mixture was stirred at room temperature for 16 h under argon. The reaction mixture was then poured over a pad of Celite and eluted with ethyl acetate. The eluant was washed with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography [silica, hexanes/ethyl acetate (1:1)] afforded a light yellow oil (710 mg, 36%): ^{1}H NMR δ 1.21 (s, 6H), 1.34, (t, J = 7.2 Hz, 3H), 2.63 (s, 2H), 3.46 (s, 6H), 4.28 (q, J = 7.2 Hz, 2H), 5.03 (s, 1H), 5.83 (s, 1H), 6.52−6.53 (m, 1H), 7.43−7.45 (m, 1H), 10.92−11.06 (brs, 1H); ^{13}C NMR δ 14.7, 29.2, 40.3, 48.4, 54.8, 59.8, 102.7, 106.9, 109.6, 116.7, 124.9, 131.7, 161.3, 165.3, 175.6; ESI-MS obsd 321.1810, calcd 321.1809 [(M + H)$^+$, M = $C_{17}H_{24}N_2O_4$].

G. Synthesis of Dihydrodipyrrin-Acetal 1-Py. 2-Formyl-4-(4-pyridyl)pyrrole (2-Py). The Vilsmeier reagent was prepared by treatment of dry DMF (55 mL) with $POCl_3$ (4.0 mL, 44 mmol) at 0 °C and stirring of the resulting mixture for 10 min. In a separate flask, a solution of 3-(4-pyridyl)pyrrole (**6-Py**, 5.78 g, 40.1 mmol) in DMF (135 mmol) was treated with the freshly prepared Vilsmeier reagent at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and then 16 h at room temperature. The reaction mixture was treated with a mixture of saturated aqueous sodium acetate/ethyl acetate [400 mL, 1:1 (v/v)] and stirred for 1 h. The water phase was separated and extracted with ethyl acetate (2 × 200 mL). The combined organic phase was washed with saturated aqueous LiCl, dried (Na_2SO_4), and concentrated. Column chromatography [silica, hexanes/ethyl acetate 1:5)] afforded two separate isomeric components. The first compound eluted was the minor isomer (54.6 mg, 9%) and was not fully characterized. The second compound eluted, the title compound, was the major constituent (1.8 g, 54%): mp 222−225 °C; ^{1}H NMR (acetone-d_6) δ 7.54 (m, 1H), 7.62−7.68 (m, 2H), 7.91 (s, 1H), 8.43−8.47 (m, 2H), 9.63 (s, 1H), 11.42 (brs, 1H); ^{13}C NMR (acetone-d_6) δ 92.5, 116.9, 119.6, 124.3, 142.0, 150.4, 166.1, 179.1; Anal. Calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.59; H, 4.71; N, 16.07; ESI-MS obsd 173.0702, calcd 173.0709 [(M + H)$^+$, M = $C_{10}H_8N_2O$].

2-(2-Nitroethyl)-4-(4-pyridyl)pyrrole (3-Py). Following a general procedure,[18] a stirred mixture of **2-Py** (1.80 g, 10.5 mmol),

potassium acetate (0.82 g, 8.4 mmol), and methylamine hydrochloride (0.56 g, 8.4 mmol) in absolute ethanol (4.0 mL) was treated with nitromethane (1.44 mL, 26.5 mmol). The mixture was stirred for 2 h, whereupon water was added. The reaction mixture was filtered, and the filtered material was washed with water and a small amount of cold ethanol. The filtered material was dried under high vacuum to afford a yellow solid, which was used directly in the next step. The crude solid material was dissolved in freshly distilled THF (100 mL), and the solution was cooled to −10 °C. The solution was treated with 90% $LiBH_4$ (254 mg, 10.5 mol) all at once under vigorous stirring. The reaction mixture was stirred for ∼15 min at −10 °C, whereupon the reaction mixture was quenched by slowly adding a cold saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (1:9)] to yield a tan solid (821 mg, 36%, two steps): mp 159.5−160.5 °C; ^{1}H NMR δ 3.37 (t, J = 6.9 Hz, 2H), 4.65 (t, J = 6.9 Hz, 2H), 6.44−6.48 (m, 1H), 7.22−7.26 (m, 1H), 7.45 (d, J = 6.6 Hz, 2H), 8.39 (d, J = 6.6 Hz, 2H), 8.69 (brs, 1H); ^{13}C NMR (acetone-d_6) δ 25.6, 75.0, 104.6, 117.5, 119.4, 121.8, 129.1, 144.5, 149.3; ESI-MS obsd 218.0924, calcd 218.0924 [(M + H)$^+$, M = $C_{11}H_{11}N_3O_2$]. Anal. Calcd for $C_{11}H_{12}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.93 H, 5.09; N, 19.08.

1,1-Dimethoxy-4,4-dimethy1-6-[4-(4-pyridyl)pyrrol-2-y1]-5-nitro-2-hexanone (5-Py). Following a general procedure,[17] a mixture of **3-Py** (500 mg, 2.30 mmol) and **4** (1.10 g, 6.91 mmol, 3 equiv) was treated with DBU (1.03 mL, 6.91 mmol). The reaction mixture was stirred at room temperature for 1 h under argon. A saturated solution of cold aqueous NH_4Cl was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Column chromatography [silica, ethyl acetate] afforded an amorphous tan solid (235 mg, 27%): ^{1}H NMR δ 1.12 (s, 3H), 1.20 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H), 2.57, 2.72 (AB, ^2J = 18.6 Hz, 2H), 3.05 (ABX, ^3J = 2.2 Hz, ^2J = 15.2 Hz, 1H), 3.36 (ABX, ^3J = 12.0 Hz, ^2J = 15.2 Hz, 1H), 3.40 (s, 3H), 3.41 (s, 3H), 4.25 (t, J = 7.2 Hz, 2H), 4.35 (s, 1H), 5.23 (ABX, ^3J = 2.2 Hz, ^3J = 12.0 Hz, 1H), 6.32 (s, 1H), 7.09 (s, 1H), 7.31 (d, J = 6.13 Hz, 2H), 8.44 (d, J = 6.13 Hz, 2H), 9.37 (brs, 1H); ^{13}C NMR δ 24.4, 24.5, 26.9, 36.7, 45.3, 55.4, 94.6, 104.7, 105.5, 116.8, 119.7, 122.4, 128.5, 143.6, 149.8, 204.0; ESI-MS obsd 376.1869, calcd 376.1867 [(M + H)$^+$, M = $C_{19}H_{25}N_3O_5$].

1-(1,1-Dimethoxymethyl)-3,3-dimethy1-8-(4-pyridyl)-2,3-dihydrodipyrrin (1-Py). Following a general procedure,[18] in a first flask, a solution of **5-Py** (135 mg, 0.360 mmol) in freshly distilled THF (3.0 mL) and anhydrous MeOH (100 μL) at 0 °C was treated with NaOMe (30 mg, 1.10 mmol). The mixture was stirred and degassed by bubbling argon through the solution for 45 min. In a second flask purged with argon, $TiCl_3$ (3.3 mL, 20 wt % in 3% HCl solution, 5.2 mmol), 7.0 mL of THF, and NH_4OAc (2.5 g, 32 mmol) were combined under argon, and the mixture was degassed by bubbling argon for 45 min. Then, the first flask mixture was transferred via cannula to the buffered $TiCl_3$ mixture. The resulting mixture was stirred at room temperature for 48 h under argon at 35 °C. The reaction mixture was then poured over a pad of Celite and eluted with ethyl acetate. The eluant was washed with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated. Column chromatography [silica, hexanes/ethyl acetate (1:1)] afforded a yellow amorphous solid (35.0 mg, 30%): ^{1}H NMR δ 1.23 (s, 6H), 2.65 (s, 2H), 3.48 (s, 6H), 5.05 (s, 1H), 5.89 (s, 1H), 6.49 (s, 1H), 7.27−7.31 (m, 1H), 7.35−7.41 (m, 2H), 8.36−8.60 (m, 2H), 10.90 (brs, 1H); ^{13}C NMR δ 29.3, 40.4, 48.5, 54.8, 102.8 106.7, 107.0, 118.1, 119.6, 122.4, 132.7, 143.6, 150.1, 161.2, 175.4; ESI-MS obsd 326.1870, calcd 326.1863 [(M + H)$^+$, M = $C_{19}H_{23}N_3O_2$].

H. Synthesis of Dihydrodipyrrin-Acetal 1-AnEs. 4-(Ethoxycarbonyl)-2-formyl-3-(4-methoxyphenyl)pyrrole (2-AnEs). A solution of **6-AnEs** (15.5 g, 63.2 mmol) in DMF (16.6 mL) and CH_2Cl_2 (200 mL) under argon was cooled to 0 °C, whereupon $POCl_3$ (7.2 mL, 77.2 mmol) was added dropwise. After 1 h, the flask was warmed to room temperature and stirred overnight (∼16 h). The reaction was quenched at 0 °C with 2.5 M aqueous NaOH (690 mL). The mixture was poured into water (∼1 L) and extracted with CH_2Cl_2, and the combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed [silica, CH_2Cl_2/ethyl acetate (9:1)] to afford a white solid (11.7 g, 68%): ^{1}H NMR δ 1.23 (t, J = 7.2 Hz, 3H), 3.86 (s, 3H), 4.21 (q, J = 7.2 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.5 Hz, 2H), 7.74 (d, J = 2.5 Hz, 1H), 9.37 (s, 1H), 10.49 (brs, 1H); ^{13}C NMR δ 14.1, 55.2, 59.9, 113.1, 116.1, 123.2, 130.7, 130.8, 132.0, 137.8, 159.6, 163.6, 181.0; FAB-MS obsd 273.0995, calcd 273.1001 ($C_{15}H_{15}NO_4$). Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.03; H, 5.48; N, 5.13.

4-(Ethoxycarbonyl)-3-(4-methoxyphenyl)-2-(2-nitroethyl)pyrrole (3-AnEs). Following a general procedure,[11] a mixture of **2-AnEs** (11.7 g, 42.8 mmol), acetic acid (1.4 mL, 5.43 mmol), *n*-propylamine (1.8 mL, 21.9 mmol) and nitromethane (7.0 mL, 128 mmol) in THF/MeOH (5:1) under argon was stirred at room temperature for 17 h. CH_2Cl_2 was added, and the reaction was quenched with brine. The organic layer was dried (Na_2SO_4) and concentrated. The residue was dissolved in $CHCl_3$/2-propanol (280 mL, 3:1), and 51 g of silica gel was added. $NaBH_4$ (3.24, 85.6 mmol) was added in portions at room temperature, and the mixture was stirred for 2 h. The reaction mixture was filtered, and the filter cake was washed with CH_2Cl_2/MeOH (9:1). The filtrate was concentrated. Crystallization from ethyl acetate/hexanes (1:2) afforded the title compound (4.42 g, 32%): ^{1}H NMR δ 1.17 (t, J = 7.1 Hz, 3H), 3.19 (t, J = 6.3 Hz, 2H), 3.83 (s, 3H), 4.13 (q, J = 7.1 Hz, 2H), 4.41 (t, J = 6.3 Hz, 2H), 6.92 (d, J = 8.3 Hz, 2H), 7.18 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 2.5 Hz, 1H), 8.58 (s, 1H); ^{13}C NMR δ 14.2, 23.4, 55.2, 59.5, 75.1, 113.4, 115.3, 123.7, 124.0, 125.0, 126.4, 131.2, 158.6, 164.5; FAB-MS obsd 318.1214, calcd 318.1216 ($C_{16}H_{18}N_2O_5$). Anal. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.31; H, 5.77; N, 8.65.

6-[4-(Ethoxycarbonyl)-3-(4-methoxyphenyl)pyrrol-2-yl]-1,1-dimethoxy-4,4-dimethyl-5-nitro-2-hexanone (5-AnEs). A mixture of **3-AnEs** (3. 86 g, 12.1 mmol) and **4** (2.3 g, 15 mmol) was treated with DBU (2.7 mL, 18 mmol). CH_3CN (15 mL) was added to the reaction mixture to dissolve the nitroethylpyrrole compound completely. The reaction mixture was stirred at room temperature for 15 h, diluted with ethyl acetate (40 mL), and washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated. The resulting oil was chromatographed [silica, CH_2Cl_2/ethyl acetate (9:1)] to afford the title compound (3.17 g, 55%): ^{1}H NMR δ 0.99 (s, 3H), 1.02 (s, 3H), 1.17 (t, J = 7.2, 3H), 2.52 (m, 2H), 3.06 (m, 2H), 3.38 (s, 6H), 3.81 (s, 3H), 4.13 (q, J = 7.1 Hz, 2H), 4.30 (s, 2H), 4.98 (m, 1H), 6.91 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 3.2 Hz, 1H), 8.91 (s, 1H); ^{13}C NMR δ 14.1, 23.5, 23.7, 24.6, 36.2, 44.5, 54.8, 55.0, 59.2, 74.3, 94.5, 104.2, 113.1, 114.7, 123.8, 124.9, 126.5, 131.1, 131.2, 158.3, 164.7, 203.2; FAB-MS obsd 476.2151, calcd 476.2159 ($C_{24}H_{32}N_2O_8$).

8-(Ethoxycarbonyl)-1-(1,1-dimethoxymethyl)-3,3-dimethyl-7-(4-methoxyphenyl)-2,3-dihydrodipyrrin (1-AnEs). Following a general procedure,[11] a solution of **5-AnEs** (500 mg, 1.05 mmol) in anhydrous THF (12.2 mL) under argon was treated with NaOMe (283 mg, 5.25 mmol). The reaction mixture was degassed by bubbling argon through the solution for 10 min and then stirred for 1 h at room temperature. In a second flask, $TiCl_3$ [8.6 wt % $TiCl_3$ in 28 wt % HCl, 9.54 g, 5.3 mmol], H_2O (42 mL), NH_4OAc (40.0 g, 519 mmol), and THF (2.8 mL) were combined. The mixture was degassed by bubbling argon for 10 min. The solution in the first flask containing the nitronate anion of **5-AnEs** was transferred via a cannula to the buffered $TiCl_3$ mixture in the second flask. The resulting mixture was stirred at room temperature for 5 h under argon. Then, the mixture was

poured into a vigorously stirred solution of saturated aqueous $NaHCO_3$ (320 mL) plus ethyl acetate (110 mL). After 20 min, the mixture was extracted with ethyl acetate. The combined organic layers were dried ($NaSO_4$) and concentrated. The resulting oil was chromatographed [silica, hexanes/ethyl acetate (1:1)] to afford the title compound (196 mg, 44%): ^{1}H NMR δ 1.14 (s, 6H), 1.20 (t, J = 7.0 Hz, 3H), 2.62 (s, 2H), 3.46 (s, 6H), 3.85 (s, 3H), 4.16 (q, J = 7.0 Hz, 2H), 5.04 (s, 1H), 5.78 (s, 1H), 6.94 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 7.53 (m, 1H), 11.17 (s, 1H); ^{13}C NMR δ 14.2, 28.9, 40.2, 48.2, 54.2, 55.1, 59.2, 102.5, 105.2, 112.9, 114.3, 124.2, 125.2, 126.8, 129.3, 131.9, 158.3, 161.1, 164.8, 175.1; FAB-MS obsd 426.2172, calcd 426.2155 ($C_{24}H_{30}N_2O_5$).

I. Synthesis of Dihydrodipyrrin-Acetal 1-MeEs. 4-Ethoxycarbonyl-2-formyl-3-methylpyrrole (2-MeEs). A solution of Vilsmeier reagent was prepared by treatment of dry DMF (7.0 mL) with $POCl_3$ (1.13 mL, 12.4 mmol) at 0 °C and stirring of the resulting mixture for 10 min. In a separate flask, a solution of 3-ethoxycarbonyl-4-methylpyrrole (**6-MeEs**, 1.53 g, 10.0 mmol) in DMF (30 mL) was treated with the freshly prepared Vilsmeier reagent at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and then 2 h at room temperature. The reaction mixture was treated with a mixture of saturated aqueous potassium acetate and CH_2Cl_2 [100 mL, 1:1 (v/v)] and stirred for 30 min. The water phase was separated and extracted with CH_2Cl_2. The combined organic phase was washed (water, brine), dried (Na_2SO_4), and concentrated. The resulting solid was dissolved in warm EtOH (~10 mL) and cooled to −15 °C. The resulting solid was filtered, washed with a small amount of cold EtOH, and dried to afford a white solid with a light-pink filtrate (1.097 g, 58%). Alternatively, in lieu of recrystallization, the crude product was chromatographed [silica, CH_2Cl_2/ethyl acetate (4:1)] to obtain the product in 76% yield. Data for recrystallized sample: mp 123−125 °C; ^{1}H NMR δ 1.35 (t, J = 7.1 Hz, 3H), 2.60 (s, 3H), 4.30 (q, J = 7.1 Hz, 2H), 7.62−7.64 (m, 1H), 9.71 (s, 1H), 9.72 (brs, 1H); ^{13}C NMR (75 MHz) δ 10.2, 14.6, 60.2, 117.6, 130.6, 130.7, 134.37, 164.4, 178.6; ESI-MS obsd 182.08088, calcd 182.08117 [$(M + H)^+$, $M = C_9H_{11}NO_3$].

4-(Ethoxycarbonyl)-3-methyl-2-(2-nitroethyl)pyrrole (3-MeEs). Following a general procedure,[18] a suspension of **2-MeEs** (3.73 g, 20.6 mmol) in nitromethane (185 mL) was treated with methylamine hydrochloride (1.67 g, 24.7 mmol) and KOAc (2.23 g, 22.6 mmol). The reaction mixture was stirred at room temperature until TLC analysis showed disappearance of the starting material (~2 h). The reaction mixture was filtered. The filtered material was washed with a small amount of cold methanol and water and dried under high vacuum to afford a yellow solid which was used directly in the next step: mp 204−207 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.27 (t, J = 7.1 Hz, 3H), 2.38 (s, 3H), 4.20 (q, J = 7.1 Hz, 2H), 7.82 (s, 1H), 7.87 (d, J = 13.2 Hz, 1H), 7.96 (d, J = 13.2 Hz, 1H), 11.63 (brs, 1H). The resulting yellow solid was suspended in dry THF (80 mL), cooled to 0 °C, and treated with $LiBH_4$ (0.444 g, 20.4 mmol) and stirred at 0 °C for 75 min. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl. The resulting mixture was extracted with CH_2Cl_2. The organic extract was washed with water and brine, dried (Na_2SO_4), and concentrated. The resulting solid was dissolved in CH_2Cl_2 (with sonication) and chromatographed [silica, $CH_2Cl_2 \rightarrow CH_2Cl_2$/ethyl acetate (1:1)] to provide a yellow solid (1.77 g, 38%): mp 144−145 °C; ^{1}H NMR δ 1.33 (t, J = 7.1 Hz, 3H), 2.23 (s, 3H), 3.25 (t, J = 7.1 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 4.53 (t, J = 7.1 Hz, 2H), 7.30 (app d, J = 3.2 Hz, 1H), 8.34 (brs, 1H); ^{13}C NMR δ 10.3, 14.7, 23.5, 59.7, 75.1, 115.6, 118.2, 123.8, 123.9, 165.6; ESI-MS obsd 227.10257, calcd 227.10262 [$(M + H)^+$, $M = C_{10}H_{14}N_2O_4$].

6-(4-Ethoxycarbonyl-3-methylpyrrol-2-yl)-1,1-dimethoxy-4,4-dimethyl-5-nitrohexan-2-one (5-MeEs). Following a general procedure,[17] a mixture of **3-MeEs** (0.452 g, 2.00 mmol) and **4** (0.632 g, 4.00 mmol) was treated with DBU (0.912 g, 6.00 mmol). The resulting mixture was stirred at room temperature for 20 h. The reaction mixture was diluted with ethyl acetate, washed twice with brine, dried (Na_2SO_4), and concentrated. Column chromatography [silica, CH_2Cl_2 CH_2Cl_2/ethyl acetate (10:1)] provided a light-brown oil which slowly solidified to a light-brown solid (0.666 g, 87%): mp 95−97 °C; ^{1}H NMR δ 1.13 (s, 3H), 1.22 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H), 2.19 (s, 3H), 2.65 (d, J = 18.5 Hz, 1H), 2.73 (d, J = 18.5 Hz, 1H), 2.94−3.00 (m, 1H), 3.21−3.30 (m, 1H), 3.41 (s, 3H), 3.42 (s, 3H), 4.22 (q, J = 7.1 Hz, 2H), 4.35 (s, 1H), 5.07−5.12 (m, 1H), 7.24 (app d, J = 3.2 Hz, 1H), 8.50 (brs, 1H); ^{13}C NMR (75 MHz) δ 10.2, 14.6, 24.36, 24.42, 24.7, 36.6, 45.2, 55.4, 59.5, 94.2, 104.9, 115.4, 118.3, 123.7, 123.8, 165.5, 203.9; ESI-MS obsd 385.1972, calcd 385.1969 [$(M + H)^+$, $M = C_{18}H_{28}N_2O_7$).

8-Ethoxycarbonyl-1-(1,1-dimethoxymethyl)-3,3,7-trimethyldipyrrin (1-MeEs). Following a general procedure,[18] a solution of **5-MeEs** (0.563 g, 1.46 mmol) in THF (13 mL) was treated with NaOMe (1.0 mL, 5.5 mmol, 30% in MeOH) and stirred for 30 min (flask 1). In a second flask a solution of $TiCl_3$ (1.35 g, 8.77 mmol) in THF (15 mL) was prepared. In a third flask, a solution of NH_4Cl (4.04 g, 76.3 mmol) in H_2O (15 mL) was prepared. The contents of the two latter flasks were degassed by three freeze−pump−thaw cycles and combined. To the resulting mixture, the contents of flask 1 were transferred by cannula, and the resulting mixture was stirred for 12 h. Saturated aqueous $NaHCO_3$ was added, and the resulting mixture was then extracted with ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. Column chromatography [silica, CH_2Cl_2/ethyl acetate (10:1] afforded a light-orange solid (0.188 g, 38%): ^{1}H NMR δ 1.23 (s, 6H), 1.34 (t, J = 7.1 Hz, 3H), 2.34 (s, 3H), 2.63 (s, 2H), 3.45 (s, 6H), 4.27 (q, J = 7.1 Hz, 2H), 5.02 (s, 1H), 5.88 (s, 1H), 7.42 (app d, J = 3.2 Hz, 1H), 10.92 (brs, 1H); ^{13}C NMR (75 MHz) δ 10.5, 14.7, 29.4, 40.5, 48.5, 54.8, 59.4, 102.8, 104.7, 115.1, 119.6, 125.1, 128.9, 160.1, 165.9, 174.8; ESI-MS obsd 335.1971; calcd 335.1965 [$(M + H)^+$, $M = C_{18}H_{26}N_2O_4$].

J. Synthesis of Dihydrodipyrrin-Acetal 1-ArEs. 4-(Ethoxycarbonyl)-2-formyl-3-(4-iodophenyl)pyrrole (2-ArEs). A solution of **6-ArEs** (4.77 g, 14.0 mmol) in DMF (4.47 mL) and CH_2Cl_2 (104 mL) under argon was cooled to 0 °C, whereupon $POCl_3$ (1.57 mL, 16.8 mmol) was added dropwise. After 1 h, the flask was warmed to room temperature and stirred overnight (~17 h). The reaction was quenched at 0 °C by the addition of 2.5 M aqueous NaOH (100 mL). The mixture was poured into water (200 mL) and extracted with CH_2Cl_2. The combined organic layers were washed (water, brine), dried (Na_2SO_4), and concentrated to give a dark brown solid. The solid was dissolved in ethyl acetate (~100 mL), and the solution was passed through a bed of silica. The collected eluant was concentrated to give a brown solid. Cooling of the solution (CH_2Cl_2/hexanes) at ~−16 °C resulted in precipitation of a white solid (2.96 g, 57%): mp 175−176 °C; ^{1}H NMR δ 1.23 (t, J = 7.2 Hz, 3H), 4.21 (q, J = 7.2 Hz, 2H), 7.20 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 3.2 Hz, 1H), 7.77 (d, J = 8.2 Hz, 2H), 9.36 (s, 1H), 9.95−10.10 (brs, 1H); ^{13}C NMR δ 14.4, 60.4, 94.6, 116.8, 130.3, 130.8, 130.9, 132.8, 136.2, 137.1, 163.4, 180.7. Anal. Calcd for $C_{14}H_{12}INO_3$: C, 45.55; H, 3.28; N, 3.79. Found: C, 45.56; H, 3.29; N, 3.69.

4-(Ethoxycarbonyl)-3-(4-iodophenyl)-2-(2-nitroethyl)pyrrole (3-ArEs). Following a general procedure,[11] a stirred solution of acetic acid (276 μL, 4.66 mmol) in methanol (0.66 mL) under argon at 0 °C was treated dropwise with *n*-propylamine (362 μL, 4.40 mL). The resulting *n*-propylammonium acetate mixture was stirred for 5 min at 0 °C and then added dropwise to a stirred solution of **2** (2.95 g, 8.00 mmol) in nitromethane (20 mL) and THF (20 mL) at 0 °C. The resulting mixture was stirred for 15 min at 0 °C and then was stirred at room temperature. The reaction was monitored with TLC analysis. After 4 h, due to incomplete reaction, the same amount of *n*-propylammonium

acetate mixture, which was prepared from acetic acid (276 μL, 4.66 mmol) and *n*-propylamine (362 μL, 4.40 mL), was added to the reaction mixture. After 2 h, CH_2Cl_2 (60 mL) was added to the reaction mixture, and the organic phase was washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated under high vacuum to afford a yellowish-brown solid. The solid was dissolved with a solution of $CHCl_3$ (40 mL) and 2-propanol (13.4 mL). Silica (9.6 g) was added to the mixture. The mixture was stirred vigorously, and $NaBH_4$ (604 mg, 16.0 mmol) was added in one batch. After 20 min, a portion of $NaBH_4$ (100 mg, 2.64 mmol) was added once more. After 20 min, TLC analysis showed complete consumption of the vinylpyrrole. The mixture was filtered, and the filter cake was washed [CH_2Cl_2/ethyl acetate (4:1)]. The filtrate was concentrated, and the resulting brown solid was dissolved in ethyl acetate (~100 mL). The solution was filtered through a bed of silica (ethyl acetate) to afford a brown solid. The solid was dissolved in ethyl acetate; the subsequent addition of hexanes afforded a white solid (1.71 g, 52%): mp 155−157 °C; ^{1}H NMR δ 1.17 (t, J = 7.2 Hz, 3H), 3.20 (t, J = 6.4 Hz, 2H), 4.13 (q, J = 7.2 Hz, 2H), 4.42 (t, J = 6.4 Hz, 2H), 7.01 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 3.2 Hz, 1H), 7.70 (d, J = 8.2 Hz, 2H), 8.67−8.77 (brs, 1H); ^{13}C NMR δ 14.4, 23.4, 59.9, 75.3, 93.0, 115.3, 123.5, 124.2, 125.4, 132.4, 134.1, 137.3, 164.5. Anal. Calcd for $C_{15}H_{15}IN_2O_4$: C, 43.50; H, 3.65; N, 6.76. Found: C, 43.23; H, 3.68; N, 6.50.

6-[4-(Ethoxycarbonyl)-3-(4-iodophenyl)pyrrol-2-yl]-1,1-dimethoxy-4,4-dimethyl-5-nitro-2-hexanone (5-ArEs). A mixture of **3-ArEs** (1.50 g, 3.62 mmol) and **4** (865 mg, 5.43 mmol) in CH_3CN (5 mL) was treated with DBU (1.62 mL, 10.9 mmol). The reaction mixture was stirred at room temperature for 24 h, diluted with ethyl acetate (45 mL), and washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated. The resulting oil was chromatographed [ethyl acetate/hexanes (1:1)] to afford a light brown oil (966 mg, 47%): ^{1}H NMR δ 1.03 (s, 3H), 1.06 (s, 3H), 1.16 (t, J = 7.2 Hz, 3H), 2.47, 2.65 (AB, ^2J = 19.0 Hz, 2H), 2.90 (ABX, ^3J = 2.4 Hz, ^2J = 15.6 Hz, 1H), 3.23 (ABX, ^3J = 11.6 Hz, ^2J = 15.6 Hz, 1H), 3.416 (s, 3H), 3.420 (s, 3H), 4.12 (q, J = 7.2 Hz, 2H), 4.30 (s, 1H), 5.11 (ABX, ^3J = 2.4 Hz, ^3J = 11.6 Hz, 1H), 7.03 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 3.2 Hz, 1H), 7.71 (d, J = 8.6 Hz, 2H), 8.38−8.46 (brs, 1H); ^{13}C NMR δ 14.4, 24.16, 24.18, 24.8, 36.7, 45.0, 55.4, 59.8, 92.8, 94.6, 104.8, 115.2, 123.7, 124.3, 125.3, 132.6, 134.2, 137.1, 164.6, 203.7; ESI-MS obsd 573.1093, calcd 573.1092 [(M + H)$^+$, M = $C_{23}H_{29}IN_2O_7$].

8-(Ethoxycarbonyl)-1-(1,1-dimethoxymethyl)-3,3-dimethyl-7-(4-iodophenyl)-2,3-dihydrodipyrrin (1-ArEs). Following a general procedure,[11] a solution of **5-ArEs** (550 mg, 0.961 mmol) in anhydrous THF (9.6 mL) under argon was treated with NaOMe (260 mg, 4.80 mmol), and the mixture was stirred for 1 h at room temperature. In a second flask, $TiCl_3$ [8.6 wt % $TiCl_3$ in 28 wt % HCl, 7.18 mL, 4.8 mmol], H_2O (38 mL), NH_4OAc (29.6 g, 384 mmol), and THF (2.4 mL) were combined. The mixture was degassed by bubbling argon for 10 min. The solution in the first flask containing the nitronate anion of **5-ArEs** was transferred via a cannula to the buffered $TiCl_3$ mixture in the second flask. The resulting mixture was stirred at room temperature for 5 h under argon. Then, the mixture was extracted with ethyl acetate. The combined organic layers were washed (5% aqueous $NaHCO_3$, water) and then dried ($NaSO_4$). The solvent was removed under reduced pressure at room temperature. The crude product was passed through a short column [alumina, hexanes/ethyl acetate (2:1)] to afford a light yellow oil (160 mg, 32%): ^{1}H NMR δ 1.15 (s, 6H), 1.20, (t, J = 7.2 Hz, 3H), 2.63 (s, 2H), 3.46 (s, 6H), 4.16 (q, J = 7.2 Hz, 2H), 5.05 (s, 1H), 5.71 (s, 1H), 7.12 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 3.2 Hz, 1H), 7.71 (d, J = 8.2 Hz, 2H), 11.17 (brs, 1H); ^{13}C NMR δ 14.5, 29.1, 40.6, 48.6, 54.8, 59.7, 92.5, 102.6, 104.9, 114.4, 123.4, 125.7, 129.7, 133.1, 134.4, 136.8, 162.1, 164.9, 176.1; ESI-MS obsd 523.1081, calcd 523.1088 [(M + H)$^+$, M = $C_{23}H_{27}IN_2O_4$].

K. Synthesis of Dihydrodipyrrin-Acetal 1-Ar. 6-[3-(4-Iodophenyl)pyrrol-2-yl]-1,1-dimethoxy-4,4-dimethyl-5-nitro-2-hexanone (5-Ar). Following a general procedure,[11] CsF (1.10 g, 9.25 mmol, freshly dried by heating to 100 °C under vacuum for 1 h) was placed in a flask under argon. A mixture of **3-Ar** (992 mg, 2.90 mmol) and **4** (4.59 g, 29.0 mmol) in dry acetonitrile (29 mL) was transferred by cannula to the flask containing CsF. The mixture was heated at 65 °C for 7 h, whereupon TLC analysis showed the reaction to be complete. The reaction mixture was filtered through a bed of alumina [ethyl acetate/hexanes (1:2)], and the filtrate was concentrated. The resulting oil was dried for 16 h under high vacuum. Purification of the solid residue by recrystallization [hexanes/CH_2Cl_2 (10:1)] gave a light brown solid (390 mg, 26%): ^{1}H NMR δ 1.09 (s, 3H), 1.19 (s, 3H), 2.54, 2.72 (AB, ^2J = 18.8 Hz, 2H), 3.15 (ABX, $^3J_{BX}$ = 2.4 Hz, $^2J_{AB}$ = 15.6 Hz, 1H), 3.40 (ABX, $^3J_{AX}$ = 12.4 Hz, $^2J_{AB}$ = 15.6 Hz, 1H), 4.41 (s, 3H), 4.42 (s, 3H), 5.24 (ABX, $^3J_{BX}$ = 2.4 Hz, $^2J_{AX}$ = 12.4 Hz, 1H,), 6.21 (t, J = 2.8 Hz, 1H), 6.68 (t, J = 2.8 Hz, 1H), 7.09 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 8.19 (brs, 1H); ^{13}C NMR δ 24.2, 24.3, 25.2, 45.1, 55.4, 91.3, 94.6, 104.8, 109.3, 118.1, 122.5, 122.7, 130.4, 136.1, 137.7, 203.8; FAB-MS obsd 500.0818, calcd 500.0808 ($C_{20}H_{25}IN_2O_5$). Anal. Calcd for $C_{20}H_{25}IN_2O_5$: C, 48.01; H, 5.04; N, 5.60. Found: C, 48.05; H, 5.05; N, 5.61.

1-(1,1-Dimethoxymethyl)-3,3-dimethyl-7-(4-iodophenyl)-2,3-dihydrodipyrrin (1-Ar). Following a general procedure,[11] a solution of **5-Ar** (150 mg, 0.300 mmol) in anhydrous THF (3.0 mL) under argon was treated with NaOMe (81 mg, 1.5 mmol), and the mixture was stirred for 1 h at room temperature. In a second flask, $TiCl_3$ [8.6 wt % $TiCl_3$ in 28 wt % HCl, 2.24 mL, 4.8 mmol], H_2O (12 mL), NH_4OAc (9.25 g, 120 mmol) and THF (0.8 mL) were combined followed by degassed by bubbling argon for 10 min. The solution in the first flask containing the nitronate anion of **5-Ar** was transferred via a cannula to the buffered $TiCl_3$ mixture in the second flask. The resulting mixture was stirred at room temperature for 5 h under argon. Then, the mixture was extracted with ethyl acetate. The combined organic layers were washed (5% aqueous $NaHCO_3$ and water) and dried ($NaSO_4$). The solvent was removed under reduced pressure at room temperature. The crude product was passed through a short column [alumina, hexanes/ethyl acetate (2:1)] to afford a light yellow solid (26 mg, 19%): mp 143−144 °C; ^{1}H NMR δ 1.20 (s, 6H), 2.63 (s, 2H), 3.46 (s, 6H), 5.04 (s, 1H), 6.03 (s, 1H), 6.27 (t, J = 2.8 Hz, 1H), 6.88 (t, J = 2.8 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 10.90 (brs, 1H); ^{13}C NMR δ 29.3, 29.9, 40.5, 48.4, 54.8, 90.9, 102.9, 105.6, 109.0, 119.5, 123.4, 127.2, 130.7, 136.7, 137.7, 160.9, 174.9; FAB-MS obsd 450.0832, calcd 450.0804 ($C_{20}H_{23}IN_2O_2$).

L. Synthesis of Dihydrodipyrrin-Acetal 1-TEs. 8-(Ethoxycarbonyl)-1-(1,1-dimethoxymethyl)-3,3-dimethyl-7-(4-methylyphenyl)-2,3-dihydrodipyrrin (1-TEs). A solution of **6-TEs** (3.70 g, 16.1 mmol) in DMF (5.14 mL) and CH_2Cl_2 (120 mL) under argon was cooled to 0 °C, whereupon $POCl_3$ (1.77 mL, 19.0 mmol) was added dropwise. After 1 h, the flask was warmed to room temperature and stirred overnight (10 h). The reaction was quenched at 0 °C by the addition of 2.5 M aqueous NaOH (100 mL). The mixture was poured into water (200 mL) and then extracted with CH_2Cl_2. The extracted organic solution was washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed [silica, CH_2Cl_2/ethyl acetate (4:1)] to give **2-TEs** as a light brown solid (2.43 g, 59%): mp 129−130 °C; ^{1}H NMR δ 1.22 (t, J = 7.2 Hz, 3H), 2.41 (s, 3H), 4.20 (q, J = 7.2 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 0.8 Hz, 1H), 9.38 (s, 1H), 9.94−10.12 (brs, 1H); ^{13}C NMR δ 14.4, 21.5, 60.3, 116.8, 128.2, 128.7, 130.4, 130.9, 137.9, 138.3, 163.6, 181.2; Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.86; H, 5.90; N, 5.44.

Following a general procedure,[11] a stirred solution of acetic acid (134 μL, 2.33 mmol) in methanol (0.33 mL) under argon at 0 °C was treated dropwise with *n*-propylamine (181 μL, 2.20 mL). The resulting *n*-propylammonium acetate mixture was stirred for 5 min at room temperature, then added dropwise to a stirred solution of **2-TEs** (1.03 g, 4.00 mmol) in nitromethane (10 mL) and THF (3.0 mL) at 0 °C. The resulting mixture was stirred for 15 min, and then stirring was continued for 3 h at room temperature. CH_2Cl_2 (30 mL) was added to the reaction mixture, and the resulting organic phase was washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated under high vacuum to afford a brownish orange solid. The solid was dissolved with a solution of $CHCl_3$ (20 mL) and 2-propanol (6.7 mL). Silica (4.8 g) was added to the mixture. The mixture was stirred vigorously, and $NaBH_4$ (302 mg, 8.00 mmol) was added in one batch. After 20 min, a further portion of $NaBH_4$ (100 mg, 2.64 mmol) was added. After 10 min, TLC analysis showed complete consumption of the vinylpyrrole. The mixture was filtered, and the filter cake was washed with CH_2Cl_2. The filtrate was concentrated and the resulting brown oil was filtered through a bed of silica (CH_2Cl_2/ethyl acetate, 4:1) to afford a brown solid. The solid was dissolved in ethyl acetate; the subsequent addition of hexanes gave **3-TEs** as a light brown solid (598 mg, 49%): mp 155−156 °C; ^{1}H NMR δ 1.16 (t, J = 7.2 Hz, 3H), 2.38 (s, 3H), 3.20 (t, J = 6.4 Hz, 2H), 4.13 (q, J = 7.2 Hz, 2H), 4.42 (t, J = 6.4 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 3.2 Hz, 1H), 8.56−8.66 (brs, 1H); ^{13}C NMR δ 14.4, 21.4, 23.5, 59.7, 75.3, 115.4, 123.9, 124.6, 125.2, 128.9, 130.2, 131.3, 136.8, 164.7; FAB-MS obsd 302.1288, calcd 302.1267 ($C_{16}H_{18}N_2O_4$).

A mixture of **3-TEs** (3.02 g, 10.0 mmol) and **4** (1.90 g, 12.0 mmol) was treated with DBU (4.49 mL, 30.0 mmol). CH_3CN (3 mL) was added to the reaction mixture to dissolve the nitroethylpyrrole compound **3-TEs** completely. The reaction mixture was stirred at room temperature for 24 h, diluted with ethyl acetate (100 mL), and washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated. The resulting oil was chromatographed [silica, ethyl acetate/hexanes (1:2)] to afford **5-TEs** as a light yellow oil (3.63 g, 79%): ^{1}H NMR δ 1.02 (s, 3H), 1.05 (s, 3H), 1.16 (t, J = 7.2 Hz, 3H), 2.37 (s, 3H), 2.46, 2.63 (AB, ^2J = 18.8 Hz, 2H), 2.96 (ABX, ^3J = 2.4 Hz, ^2J = 15.6 Hz, 1H), 3.22 (ABX, ^3J = 11.6 Hz, ^2J = 15.6 Hz, 1H), 3.397 (s, 3H), 3.400 (s, 3H), 4.08−4.16 (m, 2H), 4.30 (s, 1H), 5.06 (ABX, ^3J = 2.4 Hz, ^3J = 11.6 Hz, 1H), 7.16 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 3.4 Hz, 1H), 8.32−8.40 (brs, 1H); ^{13}C NMR δ 14.3, 21.4, 23.8, 24.0, 24.9, 36.5, 44.7, 55.06, 55.08, 59.5, 94.9, 104.5, 115.0, 124.1, 124.6, 125.0, 128.6, 130.2, 131.4, 136.3, 164.8, 203.5; FAB-MS obsd 483.2122, calcd 483.2107 [(M + Na)$^+$, M = $C_{24}H_{32}N_2O_7$].

Following a general procedure,[11] a solution of **5-TEs** (1.00 g, 2.17 mmol) in anhydrous THF (22 mL) under argon was treated with NaOMe (586 mg, 10.9 mmol). The reaction mixture was bubbled with argon for 10 min and then stirred for 1 h at room temperature (first flask). In a second flask, $TiCl_3$ [8.6 wt % $TiCl_3$ in 28 wt % HCl, 16.2 mL, 11 mmol] and H_2O (87 mL) were combined. The mixture was bubbled with argon for 10 min. Then, NH_4OAc (66.9 g, 868 mmol) was slowly added under argon bubbling to buffer the mixture to pH 6.0 (pH paper). THF (6.5 mL) was added to the dark buffered mixture. The mixture was bubbled with argon for a further 10 min. The mixture in the first flask containing the nitronate anion of **5-TEs** was transferred via a cannula to the buffered $TiCl_3$ mixture in the second flask. The resulting mixture was stirred at room temperature for 5 h under argon. Then the mixture was poured into a vigorously stirred solution of saturated aqueous $NaHCO_3$ (320 mL) and ethyl acetate (110 mL). After 20 min, the mixture was extracted with ethyl acetate. The organic layers were combined, washed with water, dried ($NaSO_4$), and concentrated. The resulting oil was chromatographed [alumina, hexanes/ethyl acetate (1:1)] to afford the title compound (**1-TEs**) as a light yellow oil (441 mg, 51%): ^{1}H NMR δ 1.14 (s, 6H), 1.20, (t, J = 7.2 Hz, 3H), 2.40 (s, 3H), 2.61 (s, 2H), 3.46 (s, 6H), 4.16 (q, J = 7.2 Hz, 2H), 5.04 (s, 1H), 5.79 (s, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 3.2 Hz, 1H), 11.14−11.22 (brs, 1H); ^{13}C NMR δ 14.5, 21.5, 29.1, 40.5, 48.5, 54.8, 59.5, 102.7, 105.6, 114.6, 124.8, 125.5, 128.5, 129.6, 131.0, 131.7, 136.2, 161.4, 165.1, 175.4; FAB-MS obsd 410.2193, calcd 410.2206 ($C_{24}H_{30}N_2O_4$); λ_{abs} (CH_2Cl_2) 341 nm.

M. Bacteriochlorin Syntheses. 5-Methoxy-8,8,18,18-tetramethyl-2,12-bis(4-methylphenyl)bacteriochlorin (MeOBC-T) by Use of $BF_3\cdot O(Et)_2$. A solution of $BF_3\cdot O(Et)_2$ (301 μL, 2.50 mmol) in CH_3CN (6 mL) was slowly added to a solution of **1-T** (338 mg, 1.00 mmol) in CH_3CN (50 mL). The reaction mixture was stirred at room temperature for 12 h under an air atmosphere. TEA (1.00 mL, 7.17 mmol) was added to the reaction mixture. Then the reaction mixture was concentrated. The residue was chromatographed [silica, 10 cm dia × 30 cm, hexanes/CH_2Cl_2 (1:1)] to afford **HBC-T** (16.1 mg, 6%), **MeOBC-T** (133 mg, 46%), and **TDC-T** (33.0 mg, 11%). Characterization data (^{1}H NMR, LD-MS, FAB-MS, absorption spectrum) of **MeOBC-T** were consistent with the previous results.[11]

3,13-Dibromo-5-methoxy-8,8,18,18-tetramethylbacteriochlorin (MeOBC-Br). A solution of **1-Br** (200 mg, 0.611 mmol, 18 mM) in anhydrous CH_2Cl_2 (34 mL) was treated first with 2,6-DTBP (2.78 mL, 12.2 mmol, 360 mM) and second with TMSOTf (560 μL, 3.07 mmol, 90 mM). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated, and the residue was chromatographed [silica, hexanes/CH_2Cl_2 (1:1)]. A single green band was collected and concentrated to give the title compound as a green solid (55 mg, 32%): ^{1}H NMR δ −1.98 (brs, 1H), −1.77 (brs, 1H), 1.93 (s, 6H), 1.94 (s, 6H), 4.35 (s, 3H), 4.40 (s, 2H), 4.42 (s, 2H), 8.50−8.56 (m, 2H), 8.72 (d, J = 2.48 Hz, 1H), 8.74−8.80 (m, 2H); ^{13}C NMR δ 30.0, 31.0, 31.2, 45.8, 46.0, 47.5, 51.9, 64.7, 96.5, 97.1, 105.4, 112.5, 124.4, 124.9, 135.7, 169.8; ESI-MS obsd 557.05222, calcd 557.05516 [(M + H)$^+$, M = $C_{25}H_{26}Br_2N_4O$]; λ_{abs} (CH_2Cl_2) 360, 369, 504, 722 nm.

8,8,18,18-Tetramethylbacteriochlorin (HBC-H) by Use of $Bi(OTf)_3$. A solution of **1-H** (65.6 mg, 0.264 mmol, 5 mM) in anhydrous CH_2Cl_2 (53 mL) was treated with $Bi(OTf)_3$ (1.73 g, 2.64 mmol, 50 mM). The reaction mixture was stirred at room temperature for 16 h. Excess TEA (100. μL, 0.717 mmol) was added to the reaction mixture. The reaction mixture was concentrated, and the residue was chromatographed [silica, CH_2Cl_2/hexanes (1:1)]. The first green band (**HBC-H**, 5.2 mg, 11%) and the second green band (**MeOBC-H**, 4.9 mg, 9%) were collected. Further elution with CH_2Cl_2 afforded a **TDC**-type macrocycle, which was not completely characterized.

5-Methoxy-8,8,18,18-tetramethylbacteriochlorin (MeOBC-H). A solution of **1-H** (422 mg, 1.70 mmol, 5 mM) in anhydrous CH_2Cl_2 (340 mL) was treated first with 2,6-DTBP (7.50 mL, 34.0 mmol, 100 mM) and second with TMSOTf (1.53 mL, 8.50 mmol, 25 mM). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated, and the residue was chromatographed [silica, CH_2Cl_2/hexanes (1:1)]. A single green band was collected (**MeOBC-H**, 150 mg, 44%). Further elution with CH_2Cl_2 did not afford any **TDC**-type macrocycle. Data for **HBC-H**: ^{1}H NMR δ −2.40 to −2.36 (brs, 2H), 1.98 (s, 12H), 4.48 (s, 4H), 8.72−8.75 (m, 2H), 8.74 (s, 2H), 8.75−8.80 (m, 2H), 8.84 (s, 2H); ESI-MS obsd 371.2225, calcd 371.2230 [(M + H)$^+$, M = $C_{24}H_{26}N_4$]; λ_{abs} (CH_2Cl_2) 339, 364, 488, 713 nm. Data for **MeOBC-H**: ^{1}H NMR δ −2.28 (brs, 1H), −2.13 (brs, 1H), 1.95 (s, 6H), 1.97 (s, 6H), 4.42 (s, 2H), 4.48 (s, 2H), 8.60−8.79 (m, 5H), 8.93 (m, 2H); ^{13}C NMR δ 31.3, 31.4, 45.8, 46.1, 47.7, 52.0, 65.4, 96.9, 97.1, 98.0, 117.4, 120.2, 122.9, 123.7, 135.6, 137.1, 137.2,

152.7, 159.7, 169.6; ESI-MS obsd 401.2330, calcd 401.2336 [(M + H)$^+$, M = $C_{25}H_{28}N_4O$]; λ_{abs} (CH_2Cl_2) 343, 353, 365, 499, 709 nm.

3,13-Bis(ethoxycarbonyl)-2,12-diethyl-8,8,18,18-tetramethylbacteriochlorin (HBC-EtEs). A solution of **1-EtEs** (742 mg, 2.13 mmol, 18 mM) in anhydrous CH_3CN (118 mL) was treated with $BF_3 \cdot O(Et)_2$ (2.1 mL, 17 mmol, 140 mM). The reaction mixture was stirred at room temperature for 16 h. Excess TEA (2.5 mL) was added to the reaction mixture. The reaction mixture was concentrated, and the residue was chromatographed (silica, CH_2Cl_2). A single green band was isolated and concentrated to afford the title compound as a purple solid (250 mg, 41%): ^{1}H NMR δ −1.43 (brs, 2H), 1.72 (t, J = 7.15 Hz, 6H), 1.74 (t, J = 7.43 Hz, 6H), 1.94 (s, 12H), 4.14 (q, J = 7.43 Hz, 4H), 4.78 (q, J = 7.15 Hz, 4H), 8.64 (s, 2H), 9.66 (s, 2H); ^{13}C NMR δ 14.9,17.9, 21.0, 31.2, 46.1, 52.1, 61.1, 94.6, 98.8, 119.2, 133.6, 135.0, 141.9, 160.7, 166.7, 171.2; ESI-MS obsd 571.3271, calcd 571.3279 [(M + H)$^+$, M = $C_{34}H_{42}N_4O_4$]; λ_{abs} (CH_2Cl_2) 353, 382, 519, 759 nm. Further elution did not afford any **TDC**-type macrocycle.

3,13-Bis(ethoxycarbonyl)-2,12-diethyl-5-methoxy-8,8,18,18-tetramethylbacteriochlorin (MeOBC-EtEs). A solution of **1-EtEs** (185 mg, 0.531 mmol, 18 mM) in anhydrous CH_2Cl_2 (30 mL) was treated first with 2,6-DTBP (2.35 mL, 10.6 mmol, 360 mM) and second with TMSOTf (0.478 mL, 2.65 mmol, 90 mM). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated, and the residue was chromatographed (silica, CH_2Cl_2). A single green band was isolated and concentrated to afford the title compound as a purple solid (64 mg, 40%): ^{1}H NMR δ −1.84 (brs, 1H), −1.56 (brs, 1H), 1.56−1.80 (m, 12H), 1.93 (s, 6H), 1.94 (s, 6H), 3.83 (d, J = 7.7 Hz, 2H), 4.15 (d, J = 7.7 Hz, 2H), 4.22 (s, 3H), 4.36 (s, 2H), 4.40 (s, 2H), 4.78 (q, J = 7.2 Hz, 4H), 8.53 (s, 1H), 8.66 (s, 1H), 9.61 (s, 1H); ^{13}C NMR δ 14.8, 14.9, 17.7, 17.9, 20.3, 21.0, 31.2, 31.3, 45.8, 46.1, 48.1, 51.9, 61.0, 62.0, 64.6, 93.8, 95.3, 97.8, 118.4, 124.5, 128.0, 132.1, 134.2, 135.1, 135.3, 135.8, 141.9, 155.9, 160.7, 166.8, 168.2, 169.1, 171.7; ESI-MS obsd 601.3384, calcd 601.3384 [(M + H)$^+$, M = $C_{35}H_{44}N_4O_5$]; λ_{abs} (CH_2Cl_2) 356, 378, 520, 739 nm. Further elution with CH_2Cl_2 did not afford any **TDC**-type macrocycle.

2,3,12,13-Tetrakis(ethoxycarbonyl)-5-methoxy-8,8,18,18-tetramethylbacteriochlorin (MeOBC-EsEs). A solution of **1-EsEs** (30 mg, 0.076 mmol, 18 mM) in anhydrous CH_2Cl_2 (4.25 mL) was treated first with 2,6-DTBP (339 μL, 1.53 mmol, 360 mM) and second with TMSOTf (69 μL, 0.38 mmol, 90 mM). The reaction mixture was stirred at room temperature for 4 days (until no starting material **1-EsEs** remained by TLC analysis). The reaction mixture was concentrated, and the residue was chromatographed (silica, CH_2Cl_2). A single purple band was collected and concentrated to give the title compound as a purple solid (16.5 mg, 63%): ^{1}H NMR δ −1.12 (brs, 1H), −0.87 (brs, 1H), 1.54−1.74 (m, 12H), 1.91 (s, 6H), 1.92 (s, 6H), 4.22 (s, 3H), 4.30 (s, 2H), 4.32 (s, 2H), 4.74 (m, 8H), 9.06 (s, 1H), 9.13 (s, 1H), 9.66 (s, 1H); ^{13}C NMR δ 14.6, 14.7, 14.7, 14.8, 30.4, 31.0, 31.1, 46.2, 46.3, 47.6, 51.6, 61.5, 62.1, 62.2, 62.4, 64.6, 98.1, 98.7, 98.9, 125.0, 127.3, 133.4, 133.9, 135.4, 136.9, 157.0, 163.5, 164.6, 165.7, 165.9, 168.2, 172.0, 174.5; ESI-MS obsd 689.3185, calcd 689.3182 [(M + H)$^+$, M = $C_{37}H_{44}N_4O_9$]; λ_{abs} (CH_2Cl_2) 360, 548, 758 nm. Further elution with CH_2Cl_2 did not afford any **TDC**-type macrocycle.

3,13-Bis(ethoxycarbonyl)-5-methoxy-8,8,18,18-tetramethylbacteriochlorin (MeOBC-Es). A solution of **1-Es** (700 mg, 2.18 mmol) in anhydrous CH_2Cl_2 (121 mL) was treated first with 2,6-DTBP (10.0 mL, 43.8 mmol) and second with TMSOTf (2.00 mL, 10.9 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated, and the residue was chromatographed (silica, CH_2Cl_2). A single green band was collected and concentrated to give the title compound as a purple solid (50 mg, 8.4%): ^{1}H NMR δ −1.67 (brs, 1H), −1.43 (brs, 1H), 1.63−1.72 (m, 6H), 1.93 (s, 6H), 1.94 (s, 6H), 4.27 (s, 3H), 4.39 (s, 2H), 4.41 (s, 2H), 4.65−4.83 (m, 4H), 8.57 (s, 1H), 8.64 (s, 1H), 8.86 (d, J = 2.48 Hz, 1H), 9.21 (d, J = 2.48 Hz, 1H), 9.68 (s, 1 H); ESI-MS obsd 545.2762, calcd 545.2758 [(M + H)$^+$, M = $C_{31}H_{36}N_4O_5$]; λ_{abs} (CH_2Cl_2) 354, 374, 524, 735 nm.

5-Methoxy-8,8,18,18-tetramethyl-2,12-bis(4-pyridyl)bacteriochlorin (MeOBC-Py). A solution of **1-Py** (33 mg, 0.10 mmol, 18 mM) in anhydrous CH_2Cl_2 (5.6 mL) was treated first with 2,6-DTBP (462 μL, 2.03 mmol, 360 mM) and second with TMSOTf (93 μL, 0.51 mmol, 90 mM). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated, and the residue was chromatographed (silica, ethyl acetate). A single green band was collected and concentrated to give the title compound as a green solid (< 1 mg, 0.7% determined spectroscopically assuming ε_{Qy} = 120000 M^{-1}cm^{-1}): ^{1}H NMR δ −1.78 (brs, 1H), −1.55 (brs, 1H), 1.96 (s, 6H), 1.98 (s, 6H), 3.68 (s, 3H), 4.37 (s, 2H), 4.40 (s, 2H), 8.02−8.08 (m, 2H), 8.09−8.13 (m, 2H), 8.63−8.67 (m, 2H), 8.67−8.70 (m, 1H), 8.77−8.80 (m, 1H), 8.83−8.90 (m, 3H), 8.94−9.02 (m, 2H); ESI-MS obsd 555.2865, calcd 555.2867 [(M + H)$^+$, M = $C_{35}H_{34}N_6O$]; λ_{abs} (CH_2Cl_2) 364, 515, 734 nm.

3,13-Bis(ethoxycarbonyl)-5-methoxy-2,12-bis(4-methoxyphenyl)-8,8,18,18-tetramethylbacteriochlorin (MeOBC-AnEs). A solution of **1-AnEs** (0.140 g, 0.329 mmol) in anhydrous CH_2Cl_2 (66 mL) was treated first with 2,6-DTBP (1.47 mL, 6.58 mmol) and second with TMSOTf (0.298 mL, 1.64 mmol). The resulting mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated and chromatographed [silica, CH_2Cl_2/ethyl acetate (10:1)] to afford a pink greenish solid (39.7 mg, 32%): ^{1}H NMR δ −1.60 (brs, 1H), −1.31 (brs, 1H), 1.36 (t, J = 7.1 Hz, 3H), 1.44 (t, J = 7.1 Hz, 3H), 1.82 (s, 6H), 1.86 (s, 1H), 4.03 (s, 3H), 4.04 (s, 3H), 4.26 (s, 3H), 4.35 (s, 2H), 4.40 (s, 2H), 4.54 (q, J = 7.1 Hz, 2H), 4.62 (q, J = 7.1 Hz, 2H), 7.25−7.28 (m, 2H + 2H, partially overlapped with the $CHCl_3$ signal), 7.85 (d, J = 8.4 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 8.44 (s, 1H), 8.55 (s, 1H), 9.58 (s, 1H); ^{13}C NMR (75 MHz) δ 14.4, 14.6, 30.9, 31.0, 45.8, 46.2, 48.1, 51.8, 55.7, 60.9, 62.0, 64.5, 96.1, 98.0, 98.2, 113.5, 114.4, 119.3, 124.7, 126.7, 128.1, 128.2, 133.06, 133.14, 133.48, 133.51, 134.6, 135.0, 135.4, 138.4, 156.4, 159.6, 159.8, 161.2, 166.6, 168.8, 169.0, 172.5; LD-MS 756.6; ESI-MS obsd 757.3588, calcd 757.3596 [(M + H)$^+$, M = $C_{45}H_{48}N_4O_7$]; λ_{abs} 360, 377, 526, 749 nm.

3,13-Bis(ethoxycarbonyl)-5-methoxy-2,8,8,12,18,18-hexamethylbacteriochlorin (MeOBC-MeEs). A solution of **1-MeEs** (70 mg, 0.21 mmol) in CH_2Cl_2 (42 mL) was treated first with 2,6-DTBP (0.930 mL, 4.14 mmol) and second with TMSOTf (0.190 mL, 1.05 mmol). The resulting mixture was stirred at room temperature for 13 h. The reaction mixture was concentrated and chromatographed (silica, CH_2Cl_2) to afford a dark-green solid (29 mg, 48%): ^{1}H NMR δ −1.83 (brs, 1H), −1.57 (brs, 1H), 1.65 (t, J = 7.2 Hz, 3H), 1.72 (t, J = 7.1 Hz, 3H), 1.94 (s, 6H), 1.95 (s, 6H), 3.40 (s, 3H), 3.66 (s, 3H), 4.24 (s, 3H), 4.38 (s, 2H), 4.42 (s, 2H), 4.75−4.83 (m, 4), 8.52 (s, 1H), 8.66 (s, 1H), 9.62 (s, 1H); ^{13}C NMR δ 11.8, 13.6, 14.8, 15.0, 31.2, 31.3, 45.8, 46.1, 48.1, 51.9, 61.0, 62.0, 64.5, 93.9, 95.6, 97.7, 119.3, 125.1, 128.1, 133.0, 134.97, 135.04, 155.9, 160.7, 166.9, 168.1, 169.0, 171.7; LD-MS obsd 573.0 ESI-MS obsd 573.3071; calcd 573.3071 [(M + H)$^+$, M = $C_{33}H_{40}N_4O_5$); λ_{abs} 357, 380, 520, 738 nm.

3,13-Bis(ethoxycarbonyl)-5-methoxy-2,12-bis(4-iodophenyl)-8,8,18,18-tetramethylbacteriochlorin (MeOBC-ArEs). A solution of **1-ArEs** (40 mg, 0.077 mmol) in anhydrous CH_2Cl_2 (4.25 mL) was treated first with 2,6-DTBP (338 mL, 1.53 mmol) and second with TMSOTf (69 mL, 0.38 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated, and the residue was chromatographed [silica, CH_2Cl_2/hexanes (2:1)]. A single purple band was collected and concentrated to give the title compound as a purple solid (13 mg, 36%): ^{1}H NMR δ −1.55 (brs, 1H), −1.27

(brs, 1H), 1.33 (t, J = 7.0 Hz, 3H), 1.44 (t, J = 7.2 Hz, 3H), 1.81 (s, 6H), 1.85 (s, 6H), 4.24 (s, 3H), 4.34 (s, 2H), 4.40 (s, 2H), 4.52 (q, J = 7.2 Hz, 2H), 4.62 (q, J = 7.2 Hz, 2H), 7.58−7.69 (m, 2H), 7.80 (d, J = 8.3 Hz, 2H), 7.98−8.13 (m, 4H), 8.35 (s, 1H), 8.47 (s, 1H), 9.60 (s, 1 H); ^{13}C NMR δ 14.4, 14.6, 30.9, 31.0, 45.9, 46.3, 48.1, 51.8, 61.1, 62.2, 64.6, 94.1, 94.7, 95.9, 98.0, 98.4, 119.3, 128.3, 132.4, 132.7, 133.7, 133.94, 134.07, 134.2, 135.0, 135.6, 135.7, 137.1, 137.2, 138.0, 157.0, 161.7, 166.2, 168.4, 169.4; ESI-MS obsd 948.1239, calcd 948.1222 ($C_{43}H_{42}I_2N_4O_5$); λ_{abs} (CH_2Cl_2) 373, 528, 751 nm.

N. Bromination and Derivatization of Bacteriochlorins. 15-Bromo-5-methoxy-8,8,18,18-tetramethylbacteriochlorin (MeOBC-H-Br[15]). A solution of **MeOBC-H** (50.0 mg, 0.125 mmol) in THF (50 mL) was treated at once with NBS (22.0 mg, 0.125 mmol, in 1.0 mL of THF) at room temperature for 1 h. TLC analysis [silica, hexanes/CH_2Cl_2 (1:1)] showed only one spot. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), concentrated and chromatographed [silica, hexanes/CH_2Cl_2 (1:1)] to afford a green solid (51 mg, 86%): ^{1}H NMR δ −2.33 (brs, 1H), −2.08 (brs, 1H), 1.95 (s, 6H), 1.96 (s, 6H), 4.40 (s, 2H), 4.48 (s, 3H), 4.50 (s, 2H), 8.63 (s, 1H), 8.68 (s, 1H), 8.70−8.75 (m, 2H), 8.95−8.99 (m, 1H), 9.00−9.04 (m, 1 H); ESI-MS obsd 478.1372, calcd 478.1363 [M^+, M = $C_{25}H_{27}N_4O$]; λ_{abs} (CH_2Cl_2) 348, 358, 369, 512, 712 nm.

5,15-Dimethoxy-8,8,18,18-tetramethylbacteriochlorin (BC-OMe[5,15]). Following a general procedure,[33] in an oven-dried Schlenk flask equipped with a stirring bar, **MeOBC-H-Br[15]** (58.4 mg, 0.122 mmol), $Pd_2(dba)_3$, bis(2-diphenylphosphinophenyl)ether (13.2 mg, 0.0244 mmol), and Cs_2CO_3 (92.0 mg, 0.244 mmol) were dried under high vacuum for 1 h. Toluene (12.2 mL) containing methanol (20 mL, 0.487 mmol) was added to the Schlenk flask, and the mixture was degassed by three freeze−pump−thaw cycles. The flask was then placed in an oil bath, and the reaction mixture was stirred at 100 °C for 24 h. After being cooled to room temperature, the reaction mixture was filtered through Celite. The filtrate was eluted with ethyl acetate, and the eluent was concentrated. Column chromatography [silica, hexanes/CH_2Cl_2 (1:1)] afforded in the following order the starting material (11 mg), debrominated starting material **MeOBC-H** (17 mg), and the title compound (15 mg, 29%): ^{1}H NMR (THF-d_8) δ −2.38 (brs, 2H), 1.96 (s, 12H), 4.41 (s, 4H), 4.45 (s, 6H), 8.70−8.75 (m, 1H), 8.75 (s, 1H), 8.89−8.96 (m, 1 H); ^{1}H NMR (CD_2Cl_2) δ −2.36 (brs, 2H), 1.97 (s, 12H), 4.42 (s, 4H), 4.48 (s, 6H), 8.71 (s, 2H), 8.72−8.77 (m, 2H), 8.91−9.01 (m, 2H); ESI-MS obsd 431.2435, calcd 431.2442 [(M + H)$^+$, M = $C_{26}H_{30}N_4O_2$]; λ_{abs} (CH_2Cl_2) 347, 357, 367, 510, 707 nm. Note: the title compound is only sparingly soluble in a wide range of solvents including ethyl acetate, THF, acetone, DMF, DMSO, and carbon disulfide.

15-Bromo-3,13-bis(ethoxycarbonyl)-5-methoxy-8,8,18,18-tetramethylbacteriochlorin (MeOBC-Es-Br[15]) and 12-Bromo-3,13-bis(ethoxycarbonyl)-5-methoxy-8,8,18,18-tetramethylbacteriochlorin (MeOBC-Es-Br[12]). A solution of **MeOBC-Es** (16 mg, 0.030 mmol) in THF (12 mL) was treated at once with NBS (5.3 mg, 0.030 mmol, in 100 μL of THF) at room temperature for 1 h. TLC analysis [silica, CH_2Cl_2/hexanes (4:1)] showed four spots. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed [silica, CH_2Cl_2/hexanes (4:1)] to afford four fractions: the first purple band (**MeOBC-Es-Br[12]**, 2.8 mg, 15%) was pure; the second purple band consisted of a mixture of mono- and dibromobacteriochlorins on the basis of mass spectrometric data (LD-MS m/z = 622.2, 700.1) and was not further analyzed; the third purple band was recovered starting material (**MeOBC-Es**, 4.9 mg); and the fourth purple band (**MeOBC-Es-Br[15]**, 2.4 mg, 13%) was pure. Data for **MeOBC-Es-Br[12]**: ^{1}H NMR δ −1.73 (brs, 1H), −1.44 (brs, 1H), 1.62−1.72 (m, 6H), 1.92 (s, 6H), 1.94 (s, 6H), 4.24 (s, 3H), 4.35 (s, 2H), 4.41 (s, 2H), 4.73 (q, J = 7.2 Hz, 2H), 4.81 (q, J = 7.2 Hz, 2H), 8.63 (s, 1H), 8.67 (s, 1H), 9.20−9.23 (m, 1 H), 9.68 (s, 1 H); ESI-MS obsd 623.1863, calcd 623.1864 [(M + H)$^+$, M = $C_{31}H_{35}BrN_4O_5$]; λ_{abs} (CH_2Cl_2) 354, 365, 375, 523, 740 nm. Data for **MeOBC-Es-Br[15]**: ^{1}H NMR δ −1.60 (brs, 1H), −1.39 (brs, 1H), 1.92 (s, 6H), 1.93 (s, 6H), 4.28 (s, 3H), 4.37 (s, 2H), 4.41 (s, 2H), 4.67−4.82 (m, 4H), 8.53 (s, 1H), 8.59 (s, 1H), 8.79−8.83 (m, 1H), 8.86−8.89 (m, 1H); ESI-MS obsd 623.1872, calcd 623.1864 [(M + H)$^+$, M = $C_{31}H_{35}BrN_4O_5$]; λ_{abs} (CH_2Cl_2) 366, 525, 724 nm.

15-Bromo-3,13-bis(ethoxycarbonyl)-2,12-diethyl-5-methoxy-8,8,18,18-tetramethylbacteriochlorin (MeOBC-EtEs-Br[15]). A solution of **MeOBC-EtEs** (30 mg, 0.050 mmol) in THF (20 mL) was treated with NBS (9.0 mg, 0.050 mmol, in 500 μL THF) at room temperature for 1 h. TLC analysis (silica, CH_2Cl_2) showed only one spot. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), concentrated and chromatographed (silica, CH_2Cl_2) to afford a green solid (20 mg, 59%): ^{1}H NMR δ −1.95 (brs, 1H), −1.72 (brs, 1H), 1.55−1.67 (m, 6H), 1.74 (m, 6H), 1.92 (s, 6H), 1.93 (s, 6H), 3.74−3.92 (m, 4H), 4.24 (s, 3H), 4.35 (s, 2H), 4.42 (s, 2H), 4.66−4.83 (m, 4H), 8.52 (s, 1H), 8.59 (s, 1H); ESI-MS obsd 679.2494, calcd 679.2490 [(M + H)$^+$, M = $C_{35}H_{43}BrN_4O_5$]; λ_{abs} (CH_2Cl_2) 357, 366, 375, 519, 726 nm.

O. Broad Acid Survey with Two Dihydrodipyrrin-Acetals. Each reaction was carried out in a 4-mL conical microreaction vial containing 10 mM of starting dihydrodipyrrin-acetal and 50 mM acid. When employed, additives were used at 500 mM concentrations. Each vial was equipped with a conical stir bar and fitted with a Teflon septum. Reactions were done on a 0.02 mmol scale of **1-T** or **1-Br** (commensurate with accurate weighing of solid acids). The vials and stir bars were dried in an oven (120 °C). A 10 mM solution of dihydrodipyrrin-acetal (**1-T** or **1-Br**) was prepared in the appropriate anhydrous solvent. Anhydrous solvents (CH_2Cl_2, CH_3CN) were reagent grade and were used as received.

In the case of solid acids, the appropriate amount of neat acid was placed in a microreaction vial under argon flow from an inverted glass funnel connected to an argon line. The acid was then treated with 2.00 mL of the previously prepared 10 mM dihydrodipyrrin-acetal solution. For example, for the reaction of **1-T** in CH_2Cl_2 containing $Bi(OTf)_3$, 65.6 mg (0.100 mmol) of $Bi(OTf)_3$ was placed in an oven-dried microreaction vial. Then 2.00 mL of the 10 mM solution (CH_2Cl_2) of **1-T** was added. The solid acids generally did not fully dissolve and resulted in heterogeneous reaction mixtures. Note that we use the term concentration regardless of heterogeneity for ease of comparison. In the case of liquid acids, the previously prepared 10 mM dihydrodipyrrin-acetal solution (10 mM, 2.00 mL) was placed in the microreaction vial, under argon, and treated with the appropriate amount of the acid using a microsyringe. When an additive was used, the order of addition was as follows: dihydrodipyrrin-acetal solution, (2) additive, and (3) the acid. For example, for the reaction of **1-T** with TMSOTf/2,6-DTBP in CH_2Cl_2, 2.00 mL of the previously prepared 10 mM dihydrodipyrrin-acetal solution was added to a microreaction vial, under argon. Then 225 μL of 2,6-DTBP was added, followed by 18 μL of TMSOTf.

The reactions were stirred at room temperature. The progress of the reactions was monitored by TLC and absorption spectroscopy. The first time point was typically at 30 min. If no substantial amount of bacteriochlorin was observed after 30 min, the reaction mixture was stirred overnight and checked again after 13 h, 16 h and 19 h. When bacteriochlorin formation was observed after 30 min, the reaction was checked more

frequently (after 1 h, 2 h, 3 h, and 16 h). Reactions were determined to be complete when all starting dihydrodipyrrin-acetal had been consumed (as determined by TLC) and there were no changes in the absorption spectra. The maximum duration for the self-condensation reaction was 48 h.

For TLC analysis, a 1 μL sample was directly taken from the reaction vial and spotted on the TLC plate [silica, hexanes/CH_2Cl_2 (1:1)]. TLC analysis gave information about the consumption of starting material, formation of **HBC-** and/or **MeOBC-**type macrocycles, and formation of **TDC-**type macrocycles. In general **HBC-**type macrocycles have the highest R_f value (least polar), followed by **MeOBC-**type macrocycles, then starting dihydrodipyrrin-acetal, and finally **TDC-**type macrocycles (most polar). For example, the R_f values for **HBC-Br**, **MeOBC-Br**, **1-Br**, and **TDC-Br** in hexanes/CH_2Cl_2 (1:1) are 0.75, 0.59, 0.49, and 0.25 respectively.

For absorption spectroscopic analysis, a 5 μL sample was taken from the reaction vial, diluted in 2.5 mL of CH_2Cl_2/EtOH (3:1) in a UV−vis cuvette, and checked for the presence of the characteristic bacteriochlorin Q_y absorption band (> 700 nm). Then, one drop of TEA was added to the cuvette to neutralize any putative protonated bacteriochlorins, whereupon the absorption spectrum was measured again. When the total yield of bacteriochlorin was lower than ~5% (no prominent Q_y absorption > 700 nm), the reaction mixture was not further analyzed. When there was no further progression in the reaction (based on changes in the absorption spectrum), and the total yield of bacteriochlorin was greater than ~5% (prominent Q_y absorption > 700 nm), the reaction mixture was neutralized by excess TEA, concentrated and the bacteriochlorins (if two were present) were separated by column chromatography [silica, hexanes/CH_2Cl_2 (1:1)]. The fractions containing bacteriochlorin(s) were collected, concentrated and the yield was determined spectroscopically assuming ε_{Qy} = 130,000 $M^{-1}cm^{-1}$ for **HBC**-type macrocycles and ε_{Qy} = 120,000 $M^{-1}cm^{-1}$ for **MeOBC**-type macrocycles.[11] **TDC-**type macrocycles, if present, were not isolated for the survey reactions. The intensity of the TLC spot attributed to the **TDC**-type macrocycles were visually compared to those for **HBC**-and **MeOBC**-type macrocycles by TLC analysis. The data from this study are provided in Table 1 and the Supporting Information.

P. Focused Acid Survey with Diverse Dihydrodipyrrin-Acetals. Each dihydrodipyrrin-acetal (**1**) was subjected to five Lewis acids (four of which were identified from the broad survey) under two different concentration conditions (empirically chosen),[11] for a total of 10 self-condensation conditions. The acids used were $Bi(OTf)_3$ in CH_2Cl_2, $Hf(OTf)_4$ in CH_2Cl_2, $HfCl_4$ in CH_2Cl_2, TMSOTf/2,6-DTBP in CH_2Cl_2, and $BF_3 \cdot O(Et)_2$ in CH_3CN. The concentrations employed were 5 mM **1**/50 mM acid, and 18 mM **1**/140 mM acid, except for the reactions using TMSOTf/2,6-DTBP, which were carried out at concentrations of 5 mM/25 mM/100 mM and 18 mM/90 mM/360 mM for **1**/TMSOTf/2,6-DTBP.

The reactions were carried out and analyzed in a similar fashion to the broad acid survey with the following exceptions. Reactions were done on a 0.02-mmol scale for the lower concentration (5 mM **1**/50 mM acid) reactions, and 0.036 mmol scale for the higher concentration (18 mM **1**/140 mM acid) reactions. Therefore, a 5 mM and 18 mM **1** solution was prepared in the appropriate anhydrous solvent; 4.00 mL of the 5 mM solution was added to each microreaction vial for the lower concentration reactions, and 2.00 mL of the 18 mM solution was added to each microreaction vial for the higher concentration reactions. The limit of detection by absorption spectroscopy was ~1.5% for the 5-mM reactions and ~0.4% for the 18-mM reactions. The cap of each reaction vial was sealed with Teflon tape to limit solvent evaporation during the course of the reaction. The reaction mixture and vial were weighed at the start and before quenching, which verified that there was no significant solvent loss. The data from this study are provided in Table 2 and the Supporting Information.

Q. $TiCl_3$ Reagent for Reductive Cyclization. Over the course of this study three different procedures were employed concerning the $TiCl_3$ reagent for use in the reductive cyclization reaction. (i) The earliest conditions[11,17,24,38] employed a solution containing 8.6 wt % $TiCl_3$ in 28 wt % HCl, available commercially or prepared as follows: 5.0 g of solid $TiCl_3$ (32 mmol) in a 250-mL flask was treated with 44.0 g of concentrated aqueous HCl (36.7 mL, 37.3 wt %, d = 1.19 g/mL, 0.45 mol) followed by 9.1 g of H_2O (0.51 mol). The resulting solution had a measured density of 1.20 g/mL. These conditions required large amounts of NH_4OAc to buffer the mixture to pH 6. (ii) A subsequent approach[13,18] entailed the use of solid $TiCl_3$ without HCl, which significantly reduced the amount of NH_4OAc necessary to buffer the $TiCl_3$ mixture but was cumbersome with regards to handling solid $TiCl_3$ on the open bench. (iii) The most recent procedure[18] makes use of a commercially available $TiCl_3$ solution [20 wt % in 3% HCl, d = 1.22 g/mL], which is readily handled and allows for the use of relatively small amounts of NH_4OAc as a buffering agent. While each procedure is effective, this latter approach appears superior in ease of handling $TiCl_3$ and modest buffer requirement.

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Supporting Information Available: Acid catalysis survey data; discussion of refined syntheses of **1-T** and **1-H**; X-ray data for **2-Py**; spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.