JOC The Journal of Organic Chemistry

Article

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Synthesis of 24 Bacteriochlorin Isotopologues, Each Containing a Symmetrical Pair of ^{13}C or ^{15}N Atoms in the Inner Core of the Macrocycle

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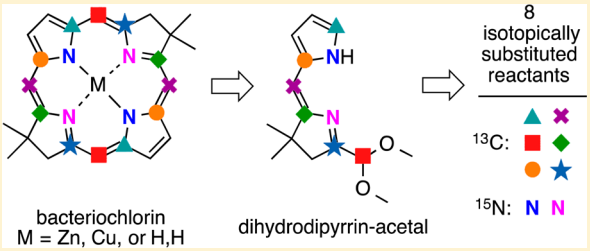
Supporting Information

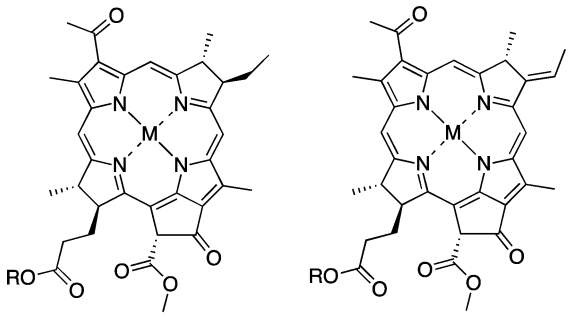
ABSTRACT: Synthetic bacteriochlorins containing site-specific isotopic substitution enable spectroscopic interrogation to delineate physicochemical features relevant to bacteriochlorophylls in photosynthesis but have been little explored. A de novo synthesis has been employed to prepare bacteriochlorins wherein each macrocycle contains a pair of ^{13}C or ^{15}N atoms yet lacks substituents other than a geminal dimethyl group in each pyrroline ring. Preparation of a dihydrodipyrrin−acetal with single-isotopic substitution gives rise to a bacteriochlorin that contains two isotopic substitutions symmetrically disposed by a 180° rotation about the normal to the plane of the macrocycle. Eight such isotopically substituted bacteriochlorins were prepared from commercially available reactants (bacteriochlorin sites): (^{13}C)paraformaldehyde (1, 11); (^{13}C)formamide (4, 14); triethyl (^{13}C)orthoformate (5, 15); $K^{13}CN$ (6, 16); $^{13}CH_3NO_2$ (9, 19); *N,N*-dimethyl(^{13}C)formamide (10, 20); (^{15}N)pyrrole (21, 23); $CH_3{}^{15}NO_2$ (22, 24). Some loss of ^{15}N upon $TiCl_3$-mediated McMurry-type ring closure of a nitro(^{15}N)hexanone is attributed to a parallel sequence of three reactions (Nef, exchange with natural-abundance NH_4OAc buffer, and Paal−Knorr ring closure) leading to the dihydrodipyrrin−acetal. Zinc and copper chelates of each bacteriochlorin also were prepared. Together, the 24 bacteriochlorin isotopologues should provide valuable benchmarks for understanding ground- and excited-state molecular physics of the macrocycles related to photosynthetic function of bacteriochlorophylls.



INTRODUCTION

Bacteriochlorophylls and their free base analogues (bacteriopheophytins) are the chief chromophores that enable energy transduction in photosynthetic bacteria (Chart 1).[1] Consequently, the characterization of the fundamental physicochemical properties of the isolated chromophores, independent of the complexities of the photosynthetic protein assemblies, has been a topic of longstanding interest. Spectroscopic studies have been paramount and include traditional optical methods (absorption and fluorescence) as well as other techniques such as electron paramagnetic resonance (EPR) and resonance Raman (RR) spectroscopy.[2−8] EPR spectroscopy provides a fundamental understanding of the spin-density distribution in the radical species, whereas RR spectroscopy affords information on the vibrational characteristics of the molecule, which may be utilized in normal-coordinate analysis. Regardless, spectroscopic interrogation of bacteriochlorophylls is limited in two ways: (1) naturally occurring bacteriochlorophylls are somewhat labile and can undergo dehydrogenation to yield the corresponding chlorins;[9] (2) the nearly full complement of peripheral substituents around the bacteriochlorin chromophore causes highly rich and congested spectra. Two simplifying methods have been resorted to, including use of porphyrins as surrogates of bacteriochlorophylls and preparation of synthetic bacteriochlorins that bear stable isotopes at designated sites.

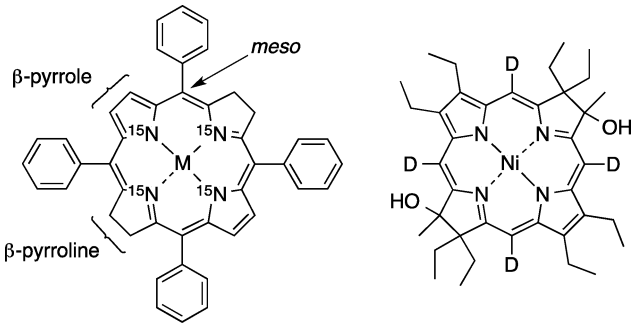
Chart 1. Natural Bacterial Photosynthetic Pigments



Received: November 9, 2013
Published: January 14, 2014

Porphyrins have long been exploited as biomimetic analogues of bacteriochlorophylls, owing to their ready accessibility and versatile synthetic malleability. Nonetheless, use of the porphyrin surrogates ignores the essential structural differences among the respective classes of tetrapyrroles; indeed, the different reduction levels of porphyrins versus bacteriochlorins (tetrahydroporphyrins) causes profound changes in physicochemical properties, which are particularly manifested in the spectral properties. To our knowledge, only two synthetic bacteriochlorin core structures and their isotopologues have been prepared for spectroscopic purposes; these include *meso*-tetraphenylbacteriochlorin and octaethylbacteriochlorin species. The *meso*-tetraphenylbacteriochlorin (**TPBC**) scaffold has proved more versatile, with reported isotopologues including the all-^{15}N (shown in Chart 2), all-meso-^{13}C, all-phenyl-d_{20}, and β-d_8 species. Fajer et al.[10] examined the cation radicals of zinc and free base **TPBC** isotopologues by EPR spectroscopy. Bocian et al.[11] performed a normal coordinate analysis of **Cu-TPBC** isotopologues based on RR spectroscopic studies. Spiro et al.[12−14] employed the nickel(II) chelate of an isotopically substituted octaethylbacteriochlorin (**Ni-OEBC**) as well as **M-TPBC** isotopologues for vibrational spectroscopic studies.

Chart 2. Representative Structures of Synthetic Isotopically Substituted Bacteriochlorins

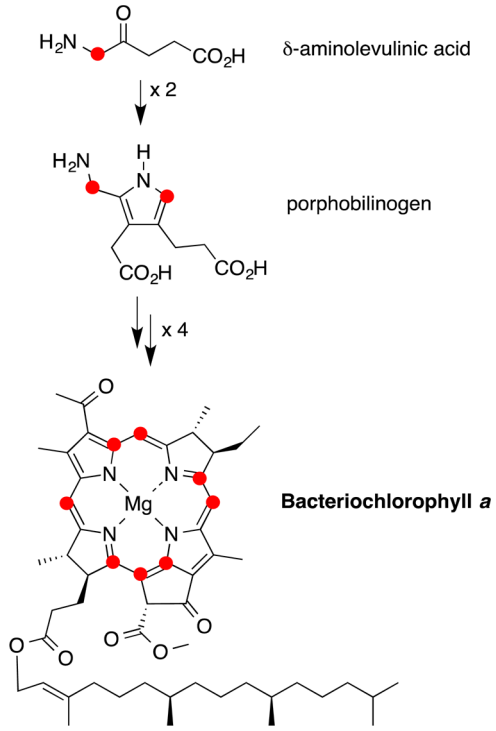


M-TPBC-all-^{15}N
M = H,H; Cu; Zn

Ni-OEBC

The synthetic routes to **M-TPBC** and **Ni-OEBC** relied on hydrogenation of *meso*-tetraphenylporphyrin[15] and transformation of octaethylporphyrin,[16] respectively. Such approaches are satisfactory for situations wherein the isotopic substitution pattern in the porphyrin gives rise to a distinct and unambiguous pattern in the bacteriochlorin (e.g., **M-TPBC-all-^{15}N** in Chart 2). On the other hand, transformation of a porphyrin that bears a single isotopic atom can result in a mixture of up to four isotopomeric bacteriochlorins. A complementary route toward isotopically substituted bacteriochlorophylls relies on biosynthetic transformations;[17] however, even with the availability of rather advanced precursors (such as δ-aminolevulinic acid or porphobilinogen) that bear site-specific isotopic substitution,[18,19] the resulting macrocycles bear isotopic atoms at numerous sites (Scheme 1). Such bacteriochlorophylls have numerous valuable applications[20] but are not generally well suited for studies aimed at developing spin-density maps or vibrational force fields because of the spectral complexity arising from multiple isotopic atoms. In this regard, no bacteriochlorins that contain only one or two isotopic atoms have yet been reported.

Scheme 1. Representative Isotopologue of Bacteriochlorophyll[a,20]



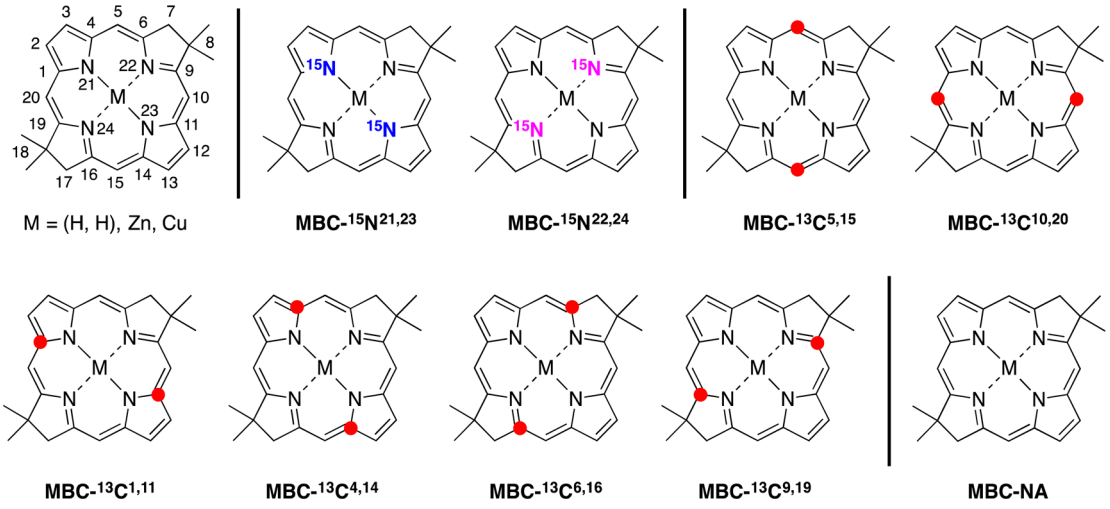
[a]The red ● denotes ^{13}C.

Methods for the synthesis of bacterichlorins have advanced significantly over the past two decades,[21] encompassing semisynthesis (beginning with naturally occurring macrocycles),[9,22,23] derivatization of intact synthetic porphyrins or chlorins,[24−28] and de novo syntheses.[29−33] Only the last method enables site-specific control over isotopic placement in the macrocycle framework. The de novo routes also incorporate a geminal dialkyl group in each pyrroline ring that stabilizes the tetrahydroporphyrin chromophore toward adventitious dehydrogenation. The route we developed relies on the acid-catalyzed self-condensation of a dihydrodipyrrin−acetal.[31] The synthetic bacteriochlorin has nominal C_{2h} symmetry (assuming a planar macrocycle and the appropriate conformations of the geminal dimethyl groups) and, save for the geminal dimethyl group in each pyrroline ring, would exhibit D_{2h} symmetry characteristic of the bacteriochlorin π framework. This synthetic route is concise, has been exploited to prepare a wide variety of substituted bacteriochlorins,[34] and accommodates numerous metal chelates.[35] These advances open the door to the use of the de novo synthetic route to prepare bacteriochlorins that bear site-specific isotopic substitution.

The sparsely substituted natural abundance bacteriochlorin **H_2BC-NA** (Chart 3), which contains no substituents other than the geminal dimethyl groups, was first prepared by debromination of the corresponding 3,13-dibromobacteriochlorin[36] and more recently by condensation of the unsubstituted dihydrodipyrrin−acetal.[34] The simple substitution pattern makes **H_2BC-NA** a valuable benchmark compound for fundamental spectroscopic studies.[36] Herein, we expanded the benchmark compound to include zinc and copper chelates (**ZnBC-NA** and **CuBC-NA**) with specific isotope substitution. The nature of the self-condensation of the dihydrodipyrrin−

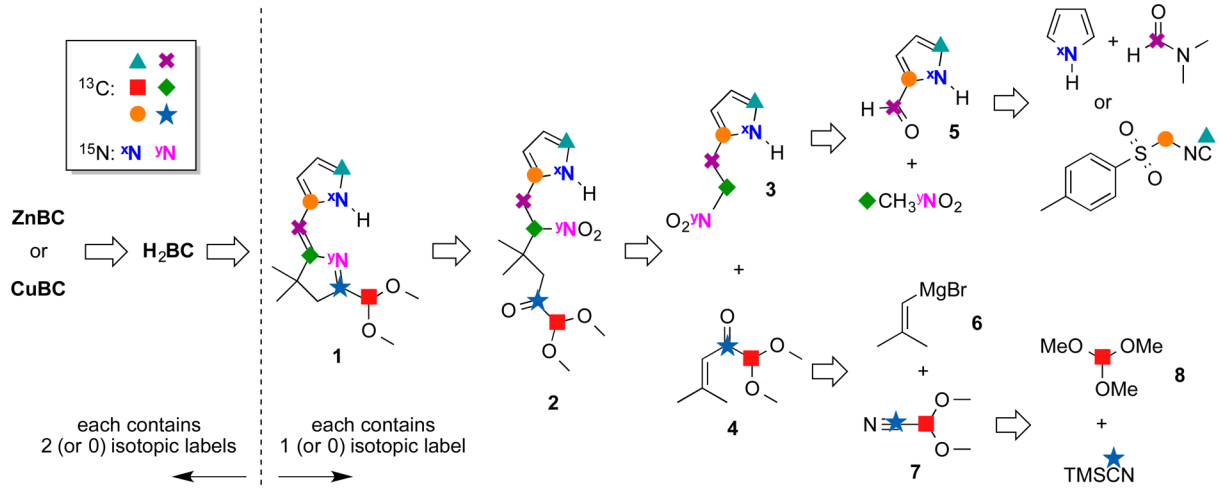
dx.doi.org/10.1021/jo402488n | J. Org. Chem. 2014, 79, 1001−1016

Chart 3. Isotopically Substituted Synthetic Bacteriochlorins[a]



[a]The red ● denotes ^{13}C.

Scheme 2. Retrosynthesis of Isotopically Substituted Bacteriochlorins



acetal leads to the introduction of isotopes in a pairwise manner. Our focus to date concerns the atoms that constitute the inner core of the bacteriochlorin, namely the 12 carbon and 4 nitrogen atoms. The inner core encompasses the entire π system excepting only the 4 β-pyrrolic carbons. Given pairwise isotopic substitution, there are 8 resulting bacteriochlorins that are "double-stamped" with isotopic atoms (for usage of this term in a different context in tetrapyrrole chemistry, see Tsay et al.[37]). Zinc chelates of bacteriochlorins yield stable anion and cation radicals and therefore are suited for EPR spectroscopic analysis. Copper bacteriochlorins afford no detectable fluorescence, which otherwise causes interference in RR spectroscopy. Accordingly, we have synthesized 8 free base bacteriochlorins with pairwise introduction of ^{13}C or ^{15}N atoms about the inner resonance frame, as well as the corresponding zinc and copper chelates. The structures of the synthetic bacteriochlorins—a pair of isotopomers with ^{15}N substitution and 6 isotopomers with ^{13}C substitution—are shown in Chart 3. Here, we report the synthesis; studies of the physicochemical properties (vibrational analysis and spin density mapping) of the 24 bacteriochlorins will be reported elsewhere.

RESULTS AND DISCUSSION

Throughout the paper we employ IUPAC nomenclature and terminology for isotopic chemistry.[38,39] Hereafter, we employ **X-NA** for the natural abundance compound, the use of braces, {**X**}, to refer to a set of isotopologues of **X-NA**, and **X** to indicate a general structure regardless of any isotopic substitution.

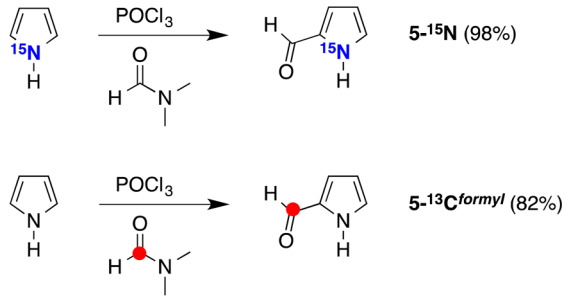
Retrosynthetic Analysis. The retrosynthesis of isotopically substituted metallobacteriochlorins is outlined in Scheme 2. The desired zinc and copper chelates are obtained by metalation of **H_2BC**,[35] which are created upon acid-catalyzed condensation of the dihydrodipyrrin−acetal **1**.[34] The dihydrodipyrrin−acetal is synthesized through a McMurry-type reductive cyclization of the nitrohexanone−pyrrole **2**, which in turn is derived from the nitroethylpyrrole **3** and the α,β-unsaturated ketone−acetal **4**.[34] The nitroethylpyrrole **3** is synthesized from nitromethane and pyrrole-2-carboxaldehyde (**5**), for which multiple routes are available. The α,β-unsaturated ketone−acetal **4** is obtained upon reaction of Grignard reagent **6** with dimethoxyacetonitrile (**7**), which in turn is prepared from trimethyl orthoformate (**8**) and TMSCN.[40]

dx.doi.org/10.1021/jo402488n | J. Org. Chem. 2014, 79, 1001−1016

Synthesis. The synthesis of dihydrodipyrrin−acetal **1-NA** has been reported twice[34,41] during the development of routes to bacteriochlorin **H_2BC-NA**. The compound 2-(2-nitroethyl)-pyrrole (**3-NA**) has served as a versatile intermediate in the synthesis of chlorins[42−44] and bacteriochlorins.[34] The synthesis of **3-NA** has been reported five times at different scales, in different degrees of purity, and with various extents of characterization, given that in some cases the product was used directly in subsequent reactions.[34,41−44] The prior syntheses were refined over the course of the work described herein to handle small quantities of expensive isotopically substituted reactants.

Pyrrole-2-carboxaldehydes. Four isotopologues of **5-NA** were synthesized: **5-^{15}N**, **5-$^{13}C^{formyl}$**, **5-$^{13}C^{2}$**, and **5-$^{13}C^{5}$**. Pyrrole-2-carboxaldehyde **5-^{15}N** was synthesized via Vilsmeier−Haack formylation[45] of (^{15}N)pyrrole with *N*,*N*-dimethylformamide. The synthesis of **5-$^{13}C^{formyl}$** is known[46] and was carried out by the same reaction of pyrrole with *N*,*N*-dimethyl(^{13}C)formamide (Scheme 3). The percentages shown in this (98%, 82%) and

Scheme 3. Synthesis of Isotopically Substituted Pyrrole-2-carboxaldehyde[a]



[a]The red ● denotes ^{13}C.

subsequent diagrams indicate isolated yields rather than isotopic purities; the latter issue is discussed in Chemical Characterization (vide infra).

The syntheses of α-^{13}C-substituted formyl-pyrroles **5-$^{13}C^{2}$** and **5-$^{13}C^{5}$** are seemingly straightforward yet challenging in practice. The difficulty stems from limited accessibility to sparsely substituted pyrroles with independent control over the 2- vs 5-positions of the ^{13}C atom and the site of formylation. Indeed, prior syntheses via Knorr,[47−51] Paal−Knorr,[52,53] Hantzsch,[54] and other[55−57] routes typically have afforded α-^{13}C-substituted pyrroles that bear multiple substituents (e.g., alkyl, carboalkoxy); such substituents are not readily removed. In cases where all substituents could be removed, independent control over the 2- vs 5-sites of the formyl group and the α-^{13}C atom is not available.[49,53] One workaround entails synthesis of a pyrrole bearing an α-carbon protective group and the desired ^{13}C atom at the same (α) or distinct (α, α') positions. In this regard, 2-(methylthio)(2-^{13}C)pyrrole was synthesized and found to undergo electrophilic aromatic substitution at the 5-position.[58] The methylthio group was subsequently removed by treatment with Raney nickel. While this approach offered potential, we turned to a route that relies on the use of ^{13}C-substituted *p*-toluenesulfonylmethyl isocyanide (TosMIC)[59] to construct the ^{13}C-substituted pyrroles.

The two isotopomers can be synthesized by the same route via isotopologues of TosMIC. TosMIC is typically synthesized from three components: paraformaldehyde, formamide, and sodium *p*-toluenesulfinate.[60] Swapping paraformaldehyde for the ^{13}C-substituted reagent will make an α-^{13}C-substituted TosMIC (**TosMIC-$^{13}C^{\alpha}$**). The same strategy has been exploited to make an α-^{14}C-labeled TosMIC.[61] Similarly, utilizing (^{13}C)formamide in the reaction will make **TosMIC-$^{13}C^{NC}$**. Thus, the corresponding ^{13}C-substituted paraformaldehyde and formamide were mixed under basic conditions (K_2CO_3)[62] for 2 h at room temperature prior to reaction with sodium *p*-toluenesulfinate in acetic acid.[60] This premixing procedure helped reduce the required amounts of ^{13}C-substituted reagents. Subsequent dehydration with $POCl_3$ gave **TosMIC-$^{13}C^{\alpha}$** (from (^{13}C)paraformaldehyde, 61%) and **TosMIC-$^{13}C^{NC}$** (from (^{13}C)formamide, 43%). The structures of **TosMIC-$^{13}C^{\alpha}$** and **TosMIC-$^{13}C^{NC}$** are shown in Scheme 4.

The isotopically substituted TosMIC compounds were employed in a standard van Leusen reaction[63] with phenyl vinyl sulfone (Scheme 4). Formation of the resulting pyrrole was found to be regioselective: initial Michael addition of the deprotonated **TosMIC-$^{13}C^{\alpha}$** or **TosMIC-$^{13}C^{NC}$** to phenyl vinyl sulfone followed by cyclization gave 3-benzenesulfonylpyrrole **9-$^{13}C^{5}$** or **9-$^{13}C^{2}$**, respectively. Vilsmeier−Haack formylation of the known pyrrole **9-NA**[63] required prolonged reflux[34] and occurred at the α-position distal to the sulfonyl substituent to yield **10-NA**. A single-crystal X-ray structure of natural abundance **10-NA** provided proof of regioselective formylation (see Figure S1 in the Supporting Information). Thus, Vilsmeier−Haack formylation of **9-$^{13}C^{5}$** or **9-$^{13}C^{2}$** gave **10-$^{13}C^{2}$** or **10-$^{13}C^{5}$**, respectively (note the change in nomenclature upon this transformation). Pyrrolecarboxaldehyde **10-NA** and each isotopologue thereof ({**10**}) were doubly protected by sequential treatment with Boc-anhydride[64] and ethylene glycol[65] to give the *N*-Boc acetal **11-NA** and {**11**}. The protected pyrroles were subjected to reductive desulfonylation by deactivated Raney nickel[66] to afford the protected pyrrole-2-carboxaldehyde **12-NA** and {**12**}. Freshly made or shelf-stored Raney nickel[67,68] generally gave yields of <20%. Other reducing agents, including AIBN,[69] NaHg,[70,71] and $Na_2S_2O_4$,[72] did not yield the desired product. Subsequent deprotection by AcOH/H_2O and NaOMe[73] gave the desired pyrrole-2-carboxaldehydes **5-$^{13}C^{2}$** and **5-$^{13}C^{5}$** with site-specific α-^{13}C substitution.

Alternative attempts to synthesize **5-$^{13}C^{2}$** and **5-$^{13}C^{5}$** entailed the use of TosMIC and ethyl acrylate followed by formylation to give the known 4-ethoxycarbonyl-2-formylpyrrole[34] and isomeric 3-ethoxycarbonyl-2-formylpyrrole. In an exploratory study with natural abundance reactants, the isomers were separated but attempts at thermal decarboxylation,[74] iododecarboxylation,[75] or catalytic decarboxylation[76] did not yield the desired product.

α,β-Unsaturated Ketone−Acetals. Two isotopologues of the α,β-unsaturated ketone−acetal **4-NA** were required. Reaction of K^{13}CN and bis(trimethylsilyl) sulfate afforded TMS^{13}CN.[77] By an established route,[40] reaction of TMS^{13}CN with trimethyl orthoformate and catalytic BF_3·OEt_2 gave 1,1-dimethoxyacetonitrile **7-$^{13}C^{CN}$**. Treatment of the latter with Grignard reagent **6** followed by hydrolysis gave ketone−acetal **4-$^{13}C^{2}$** in 19% overall yield (Scheme 5, left sequence).

Introduction of the ^{13}C atom at position 1 requires use of trimethyl (^{13}C)orthoformate, which to our knowledge was not commercially available. Accordingly, the commercially available triethyl (^{13}C)orthoformate (**8Et-$^{13}C^{1}$**) was used instead. The reaction sequence proceeded uneventfully, with conversion of **8Et-$^{13}C^{1}$** to 1,1-diethoxy (1-^{13}C)acetonitrile (**7Et-$^{13}C^{1}$**), which

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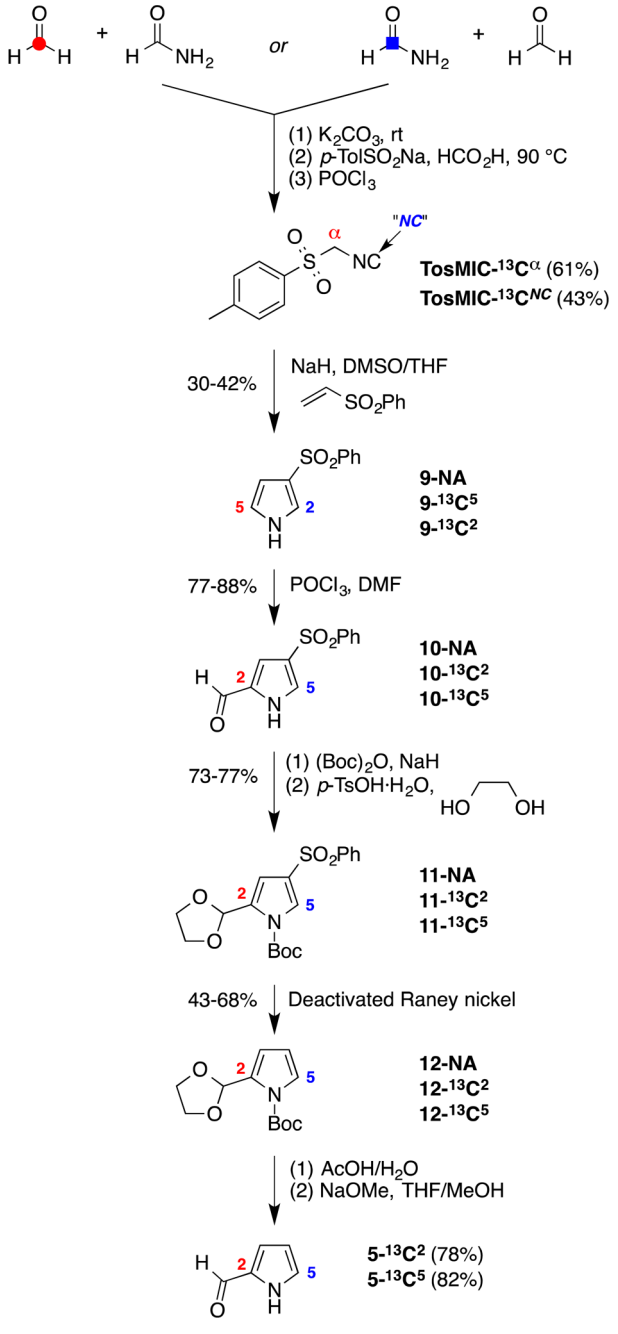
Scheme 4. Syntheses of α-^{13}C-Substituted Pyrrole-2-carboxaldehydes[a]

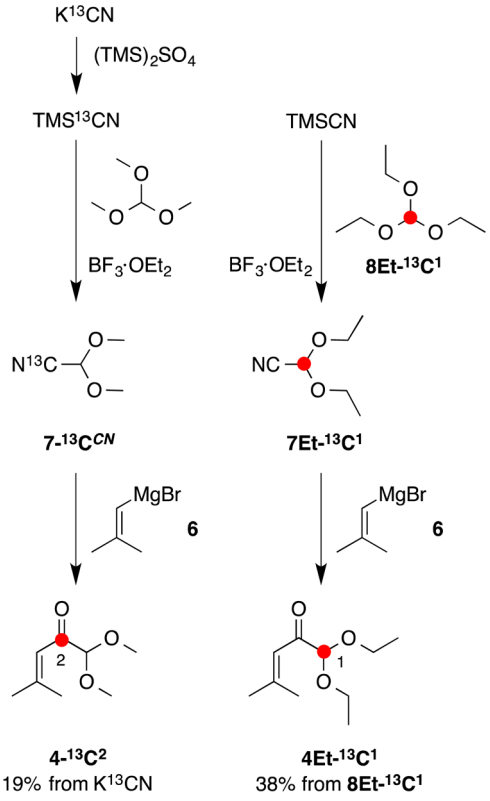


[a]The red ● and the blue ■ denote ^{13}C.

upon reaction with Grignard reagent **6** followed by hydrolysis gave **4Et-^{13}C^{1}** in 38% overall yield (Scheme 5, right sequence).

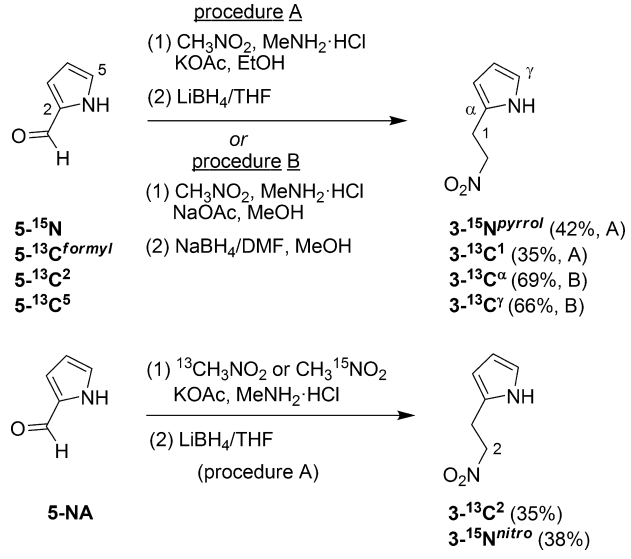
Nitroethylpyrroles. Four isotopologues {**5**} were transformed to the corresponding nitroethylpyrrole {**3**} via nitroaldol (Henry) condensation with CH_3NO_2 and subsequent borohydride reduction (Scheme 6). Compounds **3-^{13}C^{2}** (a known compound)[78] and **3-^{15}N^{nitro}** were obtained by reaction of **5-NA** with $^{13}CH_3NO_2$ and $CH_3{}^{15}NO_2$, respectively. Drawing on prior syntheses of **3-NA**,[34,43] we employed two procedures that differ chiefly in reaction time and workup procedure. Procedure A employed a 2.5 h Henry reaction with partial purification of the nitrovinylpyrrole prior to $LiBH_4$ reduction (35–42% yields), whereas a longer reaction time

Scheme 5. Synthesis of Isotopically Substituted α,β-Unsaturated Ketone–Acetals[a]



[a]The red ● denotes ^{13}C.

Scheme 6. Synthesis of Various Isotopically Substituted Nitroethylpyrroles



(12 h) and direct addition of $NaBH_4$ to the nitrovinylpyrrole constituted procedure B (66, 69% yields).

Dihydrodipyrrin–Acetals. Each nitroethylpyrrole isotopologue {**3**} was respectively reacted with α,β-unsaturated ketone **4-NA** via Michael addition[41] to give the corresponding nitrohexanone–pyrrole {**2**} (Scheme 7). Conversely, **4-^{13}C^{2}**, **4Et-^{13}C^{1}**, or known compound[40] **4Et-NA** under the same conditions with **3-NA** afforded nitrohexanone–pyrrole **2-^{13}C^{2}**,

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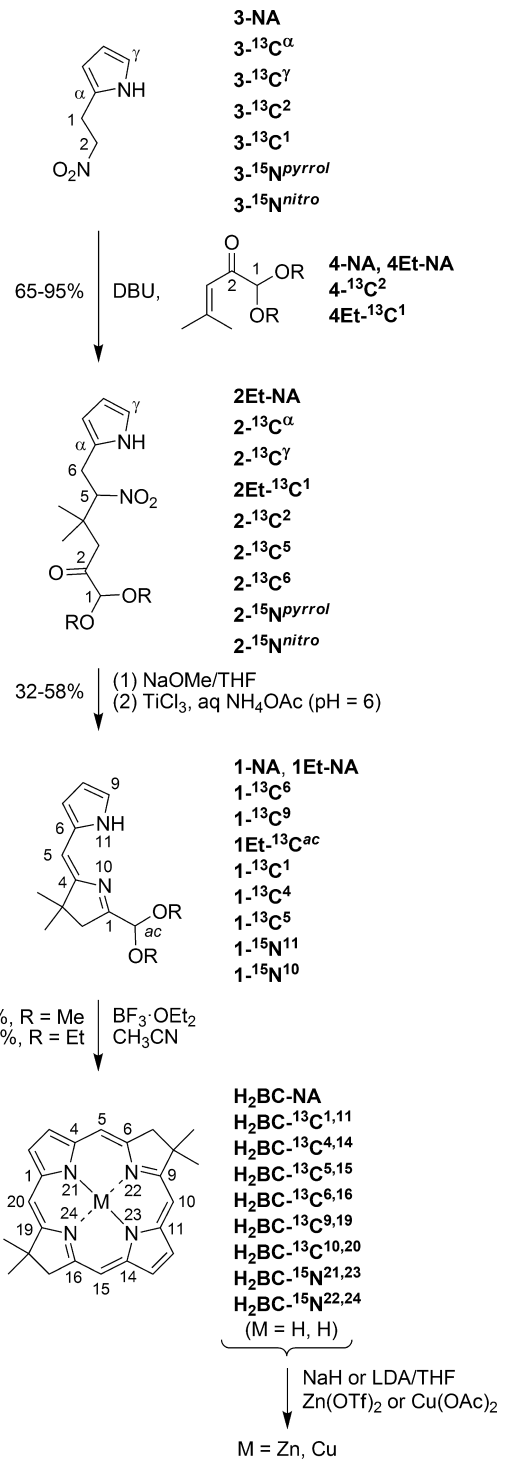
Scheme 7. Synthesis of Isotopically Substituted Bacteriochlorins[a]



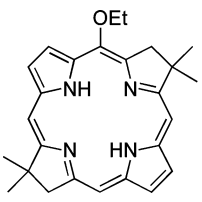
[a]See Chart 3 for individual bacteriochlorin structures.

2Et-^{13}C^{1}, or **2Et-NA**, respectively. Compound **4Et-NA** was carried through the entire reaction sequence leading to bacteriochlorins as a prelude to the use of the isotopologue **4Et-^{13}C^{1}**. The prior synthesis of nitrohexanone−pyrrole **2-NA** was achieved in 25% overall yield (upon three steps of nitro-aldol condensation, reduction, and Michael addition) from pyrrole-2-carboxaldehyde.[34] The procedural improvements herein (see the Supporting Information) gave overall yields ranging from 29% to 66% for conversion of pyrrole-2-carboxaldehyde isotopologues {**5**} to {**2**}. (Note the change in nomenclature along the series **3** → **2** → **1**.)

Each of the eight resulting isotopologues {**2**} as well as **2Et-^{13}C^{1}** and **2Et-NA** underwent McMurry-type cyclization to give the corresponding dihydrodipyrrin−acetal isotopologues {**1**}, **1Et-^{13}C^{ac}**, and **1Et-NA**, respectively. The cyclization employs $TiCl_3$ in buffered aqueous/THF solution; such a mixture was first described by McMurry for the synthesis of Δ^1-pyrrolines,[79] was adopted by Battersby for the synthesis of the 1-methyldihydrodipyrrins in the preparation of the natural chlorin Bonellin,[80] and was further modified by us for synthesis of hydrodipyrrins in routes to chlorins[42,81] and bacteriochlorins.[31,34,82] The amount of buffer required depends on the nature of the $TiCl_3$ source (powder, 3% HCl solution, or 28% HCl solution),[82] as described in the Supporting Information. We employed 6 equiv of $TiCl_3$ (20 wt % in 3% HCl solution) and 100−150 equiv of NH_4OAc per nitrohexanone−pyrrole **2**.

Bacteriochlorins. Bacteriochlorin formation is achieved by self-condensation of a dihydrodipyrrin−acetal under acidic conditions. The condensation of two dihydrodipyrrin−acetal molecules liberates three molecules of methanol and affords the monomethoxybacteriochlorin.[40] We have carried out extensive studies of acid catalysis and identified mild conditions that afford the monomethoxybacteriochlorin in reasonable yields (~40% or greater). On the other hand, the reaction in the presence of a strong acid typically affords the bacteriochlorin lacking any methoxy substituent in addition to the monomethoxybacteriochlorin, with lower total yields of macrocycles. Indeed, the only prior condensation of **1-NA** employed $Bi(OTf)_3$ in CH_2Cl_2 and afforded the free base bacteriochlorin lacking the methoxy group (**H_2BC-NA**, 11%) and the monomethoxybacteriochlorin (9%).[34] Here, we employed catalysis by $BF_3{\cdot}OEt_2$ in CH_3CN at room temperature[31] to afford {**H_2BC**} and **H_2BC-NA** (from **1-NA**). In each case, the free base bacteriochlorin was readily obtained as an intense green band by a single chromatography procedure. Yields ranged from 7 to 16%, with little methoxybacteriochlorin detected for the lower-yielding reactions and only small quantities detected for the higher-yielding reactions. Regardless, the desired bacteriochlorin (lacking the methoxy substituent) was readily isolated. The scale of reaction typically afforded 20−70 mg of each free base bacteriochlorin. In the case of macrocycle formation from diethyl acetal **1Et-NA** (or **1Et-^{13}C^{ac}**), the reaction also gave the respective ethoxy-substituted bacteriochlorin **EtOBC-NA** shown in Chart 4 (or

Chart 4. Structure of EtOBC-NA



EtOBC-NA

EtOBC-^{13}C^{5,15}, not isolated but provisionally assigned). The yields of **H_2BC-NA** and **H_2BC-^{13}C^{5,15}** from **1Et-NA** and **1Et-^{13}C^{ac}** are significantly lower (3−5%) than those from the corresponding dimethyl acetal {**1**} (7−16%).

Bacteriochlorins are metalated with substantially greater difficulty than are chlorins or porphyrins.[35] The metalation of bacteriochlorins is facilitated by the presence of electron-

dx.doi.org/10.1021/jo402488n | J. Org. Chem. 2014, 79, 1001−1016

withdrawing substituents. In the absence of any such substituents, metalation has recently been achieved by treatment of the bacteriochlorin with NaH or LDA followed by the metal salt.[35] Here, each free base macrocycle was treated with NaH (or LDA) in THF containing $Cu(OAc)_2$ or $Zn(OTf)_2$ to give the desired copper or zinc chelate. The metallobacteriochlorins were typically isolated in pure form without chromatography (Scheme 7). The metalation was readily observed by the bathochromic shift of the long-wavelength absorption (Q_y) band. The intensity ($\varepsilon \approx 120000$ M^{-1} cm^{-1}) and sharpness (full width at half-maximum (fwhm) = 12 nm) of the Q_y band of the free base bacteriochlorin and the shift from 713 to 723 nm (zinc chelate, fwhm = 14 nm) or 728 nm (copper chelate, fwhm = 19 nm) provided a very clear and reliable indicator of the completion of the metalation process.

Chemical Characterization. {**1**}−{**5**}, {**9**}−{**12**}, {**H_2BC**} (as well as **EtOBC-NA**), {**ZnBC**}, and {**CuBC**} were all characterized by electrospray ionization mass spectroscopy (ESI-MS). Each isotopically substituted compound showed the correct molecular ion peak (except for **5-^{15}N** and {**TosMIC**}). ESI-MS was also used to assess the integrity of isotopic incorporation at the designated sites of the bacteriochlorin isotopologues (vide infra).

{**1**}−{**5**}, {**9**}−{**12**}, and {**H_2BC**} were also all characterized by ^{1}H NMR and ^{13}C NMR spectroscopy. Each isotopically substituted compound showed the expected splitting pattern upon ^{1}H NMR spectroscopy and an enhanced signal upon ^{13}C NMR spectroscopy. All isotopologues {**ZnBC**} (as well as **EtOBC-NA**) were characterized by ^{1}H NMR spectroscopy and absorption spectroscopy. The isotopologues {**CuBC**} were not characterized by NMR spectroscopy, given the paramagnetism of the copper chelate. The availability of the macrocycles with site-specific ^{13}C substitution enables unambiguous determination of the NMR assignments for the bacteriochlorin skeleton. In bacteriochlorins the meso protons and β-pyrrole protons resonate in a very narrow region (~8.73−8.83 ppm for **H_2BC-NA**; 8.60−8.65 ppm for **ZnBC-NA**). While ^{1}H NMR assignments can be made without isotopic substitution, the ^{13}C NMR assignments are far more challenging, given the large number of quaternary carbons. The ^{1}H and ^{13}C NMR chemical shifts for each site of ^{13}C substitution in the isotopologues {**H_2BC**} are given in Table 1. The ^{1}H NMR assignments also are provided for {**ZnBC**}.

The ^{15}N-substituted compounds ({**1**}−{**3**} and {**H_2BC**}) were characterized by ^{15}N NMR spectroscopy. The ^{15}N chemical shifts (ppm, in THF-d_8 at 298 K referenced to external nitromethane) are characteristic for the distinct types of nitrogen-containing groups: ^{15}N-pyrrole (**3-^{15}N^{pyrrol}**, −228; **2-^{15}N^{pyrrol}**, −228; **1-^{15}N^{11}**, −229; **H_2BC-^{15}N^{21,23}**, −249); ^{15}N-nitroalkyl (**3-^{15}N^{nitro}**, 6; **2-^{15}N^{nitro}**, 10); ^{15}N-pyrroline (**1-^{15}N^{10}**, −58; **H_2BC-^{15}N^{22,24}**, −82). The in-depth NMR analyses of each isotopologue {**H_2BC**} will be reported elsewhere.

The bacteriochlorins {**H_2BC**} (as well as **EtOBC-NA**), {**ZnBC**}, and {**CuBC**} were characterized by absorption spectroscopy, where each compound gave the characteristic bacteriochlorin features of strong bands in the near-UV region and a strong band in the near-infrared spectral region.[8] The copper bacteriochlorins gave λ_{abs} 728 nm and also were examined by fluorescence spectroscopy to confirm the absence of fluorescence.

Integrity of Isotopic Incorporation. Free base bacteriochlorins typically afford peaks due to both the molecular ion (M^+) and the protonated molecule $(M + H)^+$ upon ESI-MS analysis. On the other hand, the zinc and copper chelates of bacteriochlorins typically exhibit solely the molecular ion (M^+). Consequently, interpretation of the isotopic incorporation by ESI-MS is quite complicated for the free base bacteriochlorins but can be achieved for the zinc and copper chelates {**ZnBC**} and {**CuBC**}. Such comparisons are posited on the assumptions of (1) equal ionization efficiencies of isotopologues and (2) peak intensities as a reliable measure of relative ion abundance.[83] The following presentation concerns data for the zinc chelates; the same findings were arrived at upon examination of the data for the copper chelates.

The zinc chelate of a tetrapyrrole macrocycle generally shows a characteristic isotope pattern upon ESI-MS analysis due to the natural abundance of five stable isotopes of zinc (^{64}Zn (48.9%), ^{66}Zn (27.8%), ^{67}Zn (4.1%), ^{68}Zn (18.6%), and ^{70}Zn (0.6%)).[84] For **ZnBC-NA**, the molecular formula is $C_{24}H_{24}N_4Zn$. The pattern due to the zinc isotopes is superposed on that from the stable isotopes of ^{1}H (^{2}H 0.015%), ^{12}C (^{13}C 1.11%), and ^{14}N (^{15}N 0.37%) of the tetrapyrrole ligand.[84] For the ligand alone, the expected distribution of natural abundance ions is as follows:[85] (A + 0), 75.9%; (A + 1), 21.1%; (A + 2), 2.8%; (A + 3), 0.2%. Hence, the ESI-MS spectrum of a zinc bacteriochlorin is expected to exhibit multiple lines, with the monoisotopic (A + 0) entity constituting the base peak.

The observed ESI mass spectrum of **ZnBC-NA** is shown in Figure 1A. The accurate monoisotopic mass for **ZnBC-NA** was found at 432.128 m/z. The observed spectrum for **ZnBC-^{13}C^{1,11}** (Figure 1B) shows a peak distribution essentially identical with that of **ZnBC-NA** except for the expected shift to higher mass by 2 Da. In addition to the intense peak at 434.123 m/z, a tiny peak at 433.134 m/z corresponds to the monoisotopic mass of the bacteriochlorin substituted with only a single ^{13}C atom. No peak was observed for the monoisotopic species of the bacteriochlorin lacking any ^{13}C atoms. The spectrum of **ZnBC-^{13}C^{1,11}** is representative of those cases where the synthesis was performed without loss of isotopic integrity from that of the isotopically substituted reactant (>99% ^{13}C, >98% ^{15}N). Such examples also include

Table 1. NMR Chemical Shifts (δ) of {H_2BC} and {ZnBC}

position	{H_2BC} ^{1}H NMR[a]	{H_2BC} ^{13}C NMR[a]	{ZnBC} ^{1}H NMR[b]
		β Positions	
2, 12	8.77	121.84	8.65
3, 13	8.73	121.73	8.61
7, 17	4.47	51.4	4.46
8, 18	1.97[c]	46.0	1.98[c]
		α Positions	
1, 11	*d*	136.2	*d*
4, 14	*d*	135.3	*d*
6, 16	*d*	157.6	*d*
9, 19	*d*	169.6	*d*
		Meso Positions	
5, 15	8.83	98.7	8.60
10, 20	8.73	96.5	8.64
		NH Positions	
21, 23	−2.38	*d*	*d*

[a]In $CDCl_3$ at 298 K. [b]In THF-d_8 at 298 K. [c]Chemical shifts of the geminal dimethyl protons. [d]Not available.

dx.doi.org/10.1021/jo402488n | J. Org. Chem. 2014, 79, 1001−1016

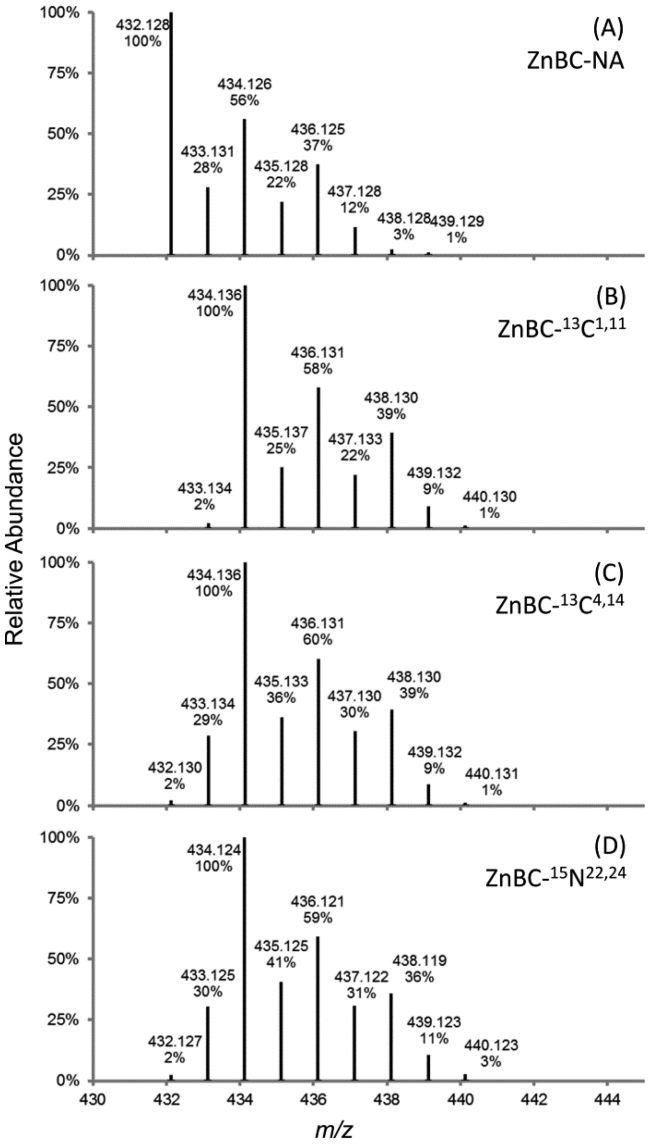


Figure 1. ESI-mass spectra of **ZnBC-NA** and three isotopologues.

ZnBC-^{13}C^{5,15}, **ZnBC-^{13}C^{6,16}**, **ZnBC-^{13}C^{9,19}**, **ZnBC-^{13}C^{10,20}**, and **ZnBC-^{15}N^{21,23}**.

On the other hand, the spectrum of **ZnBC-^{13}C^{4,14}** (Figure 1C) shows the presence of a diagnostic ion peak at 433.134 or 432.130 *m*/*z* due to the monoisotopic mass of a bacteriochlorin bearing one or no ^{13}C atom, respectively. The relative abundance of bacteriochlorins bearing 0, 1, or 2 ^{13}C atoms at the designated sites was 1.64, 23.26, or 75.10%, respectively. The overall isotopic enrichment at the designated sites for the sample of **ZnBC-^{13}C^{4,14}** thus was 87% (see the Supporting Information for the method of calculation). The isotopic loss was also found in the earliest precursor **9-^{13}C^{2}**, which contains 13% of isotopically unsubstituted species. No further isotopic loss was found for the transformation of **9-^{13}C^{2}** to the corresponding dihydrodipyrrin−acetal **1-^{13}C^{9}**. The isotopic loss apparently resulted upon formation of **TosMIC-^{13}C^{NC}** in the presence of formic acid as solvent, where formyl exchange between formic acid and (^{13}*C*)formamide may have occurred.

The spectrum of **ZnBC-^{15}N^{22,24}** (Figure 1D) also shows a peak at 433.125 or 432.127 *m*/*z* corresponding to the monoisotopic mass of a bacteriochlorin that bears one or no ^{15}N atom, respectively. The relative abundance of bacteriochlorins bearing 0, 1, or 2 ^{15}N atoms at the designated sites was 1.98, 24.29, or 73.73%, respectively. The overall isotopic enrichment at the designated sites for the sample of **ZnBC-^{15}N^{22,24}** thus was found to be 86%. The precursor **2-^{15}N^{nitro}** was found to contain only 1−2% of isotopically unsubstituted species; hence, the isotopic loss must stem from the reductive cyclization of **2-^{15}N^{nitro}** to **1-^{15}N^{10}** by exchange upon exposure to the large quantity of NH_4OAc used as buffer. The low quality of the mass spectrum of **1-^{15}N^{10}** precluded an assessment of any isotopic loss at this step. A proposal for the origin of the isotopic loss upon formation of **1-^{15}N^{10}** is shown in Scheme 8. Treatment of **2-^{15}N^{nitro}** with NaOMe affords the ^{15}N-substituted nitronate anion **I**, which upon addition to the aqueous NH_4OAc buffer can undergo a Nef reaction to give the natural abundance 2,5-diketone (**II**) with loss of an ^{15}N species (e.g., hyponitrous acid or hydroxylamine). Subsequent reaction with natural abundance NH_3 from the buffer at either ketone gives an imine or enamine (e.g., **III**), which undergoes a Paal−Knorr[86] reaction with the second carbonyl group to form the pyrroline ring of **1-NA**. (Alternatively, direct attack of NH_3 may occur on the carbon of the nitronate **I** to displace an ^{15}N species without the intermediacy of the 5-carbonyl group in **II**.) The isotopically enriched sample hence consists of an admixture of **1-^{15}N^{10}** and **1-NA**. While the $TiCl_3$-mediated Nef reaction is known,[87] the occurrence of the sequential Nef reaction, amination with NH_4OAc buffer, and Paal−Knorr reaction in parallel with the McMurry-type ring closure for this transformation was unknown prior to the isotopic studies reported herein.

CONCLUSIONS

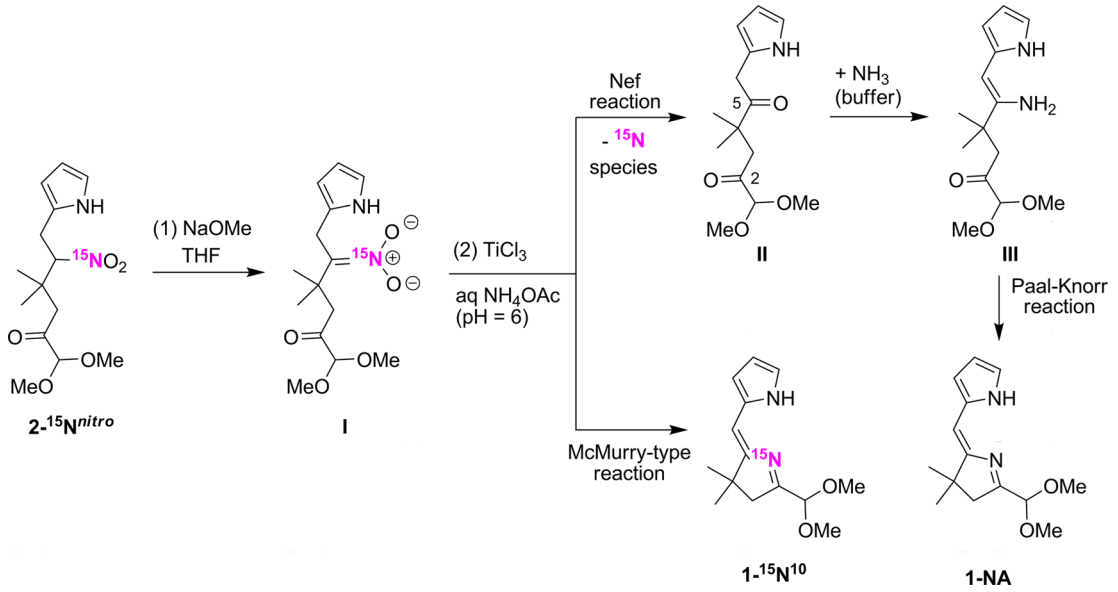
A de novo synthesis of stable bacteriochlorins has been exploited to incorporate pairs of ^{13}C or ^{15}N atoms in a site-specific manner. The concise nature of the synthesis enabled straightforward conversion of isotopically substituted small-molecule reactants (*N*,*N*-dimethyl(^{13}*C*)formamide, (^{13}*C*)-paraformaldehyde, (^{13}*C*)formamide, $^{13}CH_3NO_2$, K^{13}CN, triethyl (^{13}*C*)orthoformate, (^{15}*N*)pyrrole, and $CH_3{}^{15}NO_2$) to a set of eight free base bacteriochlorins; subsequent metalation afforded the zinc and copper chelates. Each bacteriochlorin is stable by virtue of a geminal dimethyl group in each pyrroline ring. A synthetic route to 2- or 5-^{13}C-substituted pyrrole-2-carboxaldehydes proceeded via the intermediacy of isotopically substituted TosMIC. The partial isotopic loss in two syntheses is proposed to stem from exchange processes with natural abundance species in the reaction medium. The zinc and copper chelates of the bacteriochlorin isotopologues will be examined by EPR and RR spectroscopy, respectively, to provide spin density and vibrational information germane to the function of the bacteriochlorin macrocycles in photosynthetic-like energy-transduction processes.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR (400 MHz) spectra and ^{13}C NMR spectra (100 MHz) were collected at room temperature in $CDCl_3$ unless noted otherwise. ^{15}N NMR spectroscopy (41 MHz) was performed at room temperature. The ^{15}N chemical shifts are reported relative to that of nitromethane (δ 0.0) as an indirect reference using pyrrole as a direct reference. An NMR microtube containing 8.0 M (^{15}*N*)pyrrole in THF-d_8 (70 μL) was placed in an NMR tube containing the samples in THF-d_8 (500 μL). The resonance of the pyrrole nitrogen was set to −230.1 ppm relative to nitromethane (δ

dx.doi.org/10.1021/jo402488n | J. Org. Chem. 2014, 79, 1001−1016

Scheme 8. Proposed Route for the Loss of ^{15}N upon Reductive Cyclization



0.0 ppm). The description of signals includes the following: dt, doublet of triplets; dm, doublet of multiplets. All dipole−dipole coupling constants were reported as positive values (note that J_{NH} and J_{CN} values of (^{15}N)pyrrole have been studied and reported as negative,[88,89] yet such detailed studies were not performed herein). Electrospray ionization mass spectrometry (ESI-MS) data are reported for the molecular ion or adduct ion. Absorption spectra were collected in toluene at room temperature.

The ^{15}N-substituted compounds ((^{15}N)pyrrole, $CH_3{}^{15}NO_2$) exhibited >98% ^{15}N purity. The ^{13}C-substituted compounds (*N,N*-dimethyl(^{13}C)formamide, (^{13}C)paraformaldehyde, (^{13}C)formamide, $^{13}CH_3NO_2$, $K^{13}CN$, and triethyl (^{13}C)orthoformate) exhibited 99% ^{13}C purity. NaH (dry, 95%), LDA (2.0 M solution in heptanes/THF/ethylbenzene), and Raney nickel were used as obtained commercially. Silica gel (40 μm average particle size) was used for column chromatography. All solvents were reagent grade and were used as received unless noted otherwise. THF was freshly distilled from sodium/benzophenone ketyl. Anhydrous CH_3CN and HPLC-grade CH_3CN were used as received.

Noncommercial Compounds. Compounds **1-NA**,[34] **3-NA**,[34] **4-NA**,[40] **4Et-NA**,[40] **9-NA**,[63] **ZnBC-NA**,[35] and **CuBC-NA**[35] were prepared as described in the literature.

Pyrrole-2-carboxaldehydes {5}. *(^{15}N)Pyrrole-2-carboxaldehyde (**5-^{15}N**).* Following a standard procedure,[45] *N,N*-dimethylformamide (1.61 g, 22.0 mmol) in an ice bath was slowly treated with $POCl_3$ (3.38 g, 22.0 mmol). The ice bath was removed, and the mixture was stirred for 5 min. The ice bath was replaced, and anhydrous 1,2-dichloroethane (6.8 mL) was added, followed by a solution of (^{15}N)pyrrole (1.25 g, 18.4 mmol) in 1,2-dichloroethane (6.8 mL) over 30 min. The mixture was refluxed for 15 min and then cooled to room temperature. A saturated aqueous NaOAc solution (6.9 g of NaOAc in 15 mL of deionized water) was added, and the mixture was refluxed for 15 min. The mixture was cooled to room temperature and then was diluted with diethyl ether. The mixture was washed with saturated aqueous $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and concentrated to yield a brown solid (1.73 g, 98%): mp 38−40 °C; ^1H NMR δ 6.34−6.37 (m, 1H), 7.01−7.04 (m, 1H), 7.18−7.20 (m, 1H), 9.51 (d, J = 2.6 Hz, 1H), 10.65 (dd, J = 98.4 Hz, J = 24.0 Hz, 1H); ^{13}C NMR δ 111.3 (d, J = 3.1 Hz), 122.0, 127.1 (dd, J = 14.1 Hz, J = 5.0 Hz), 132.7 (d, J = 14.5 Hz), 179.5; the sample failed to show the correct m/z peak in ESI-MS.

*Pyrrole-2-(^{13}C)carboxaldehyde (**5-$^{13}C^{formyl}$**).* The above procedure with *N,N*-dimethyl(^{13}C)formamide (1.00 g, 13.5 mmol) afforded the title compound (previously reported with limited data)[46] as a brown solid (1.07 g, 82%): mp 37−39 °C; ^1H NMR δ 6.36−6.37 (m, 1H), 7.01−7.02 (m, 1H), 7.18 (br s, 1H), 9.52 (d, J = 176 Hz, 1H), 10.28 (br s, 1H); ^{13}C NMR δ 111.3 (d, J = 4.6 Hz), 121.8 (d, J = 8.4 Hz), 126.6 (d, J = 3.1 Hz), 132.8 (d, J = 65.6 Hz), 179.4 (^{13}C); ESI-MS obsd 95.0331, calcd 95.0332 [$(M - H)^-$, M = $C_4{}^{13}CH_5NO$].

Pyrrole-2-carboxaldehydes {5} via TosMIC. *p-Toluenesulfonyl-(^{13}C)methyl Isocyanide (**TosMIC-$^{13}C^{\alpha}$**).* Following a modified procedure,[60,62] (^{13}C)paraformaldehyde (5.00 g, 161 mmol), formamide (22.5 g, 500 mmol), and K_2CO_3 (2.30 g, 16.7 mmol) were placed in a 250 mL round-bottom flask. Water (~5 mL) was added to dissolve the solid materials on the wall of the flask. The mixture was stirred at room temperature for 2 h, whereupon formic acid (52.5 g, 1.14 mol) and sodium *p*-toluenesulfinate hydrate (62.5 g, 233 mmol) were added in an alternating portionwise fashion. The mixture was heated at 90 °C for another 2 h before being poured into an ice−salt bath (400 g of ice and 40 g of salt). The mixture was extracted with CH_2Cl_2. The organic phase was washed with saturated aqueous $NaHCO_3$ solution until neutral, dried (Na_2SO_4), and concentrated to a white solid. The crude solid was placed in a 1 L round-bottom flask, to which freshly distilled THF (60 mL), anhydrous ether (24 mL), and triethylamine (56 mL) were then added. The suspension was cooled to −5 °C in an ice−salt bath. Then, a solution of $POCl_3$ (25 g, 160 mmol) in freshly distilled THF (25 mL) was added dropwise by an addition funnel at a rate such that the temperature was maintained between −5 and 0 °C. The mixture was stirred for 30 min at 0 °C, then poured into 1.5 L of ice−water with continuous stirring. The mixture was stirred for another 30 min. The resulting brown precipitate was collected by suction filtration and washed with cold water (100 mL). The collected wet product was dissolved in CH_2Cl_2, dried (Na_2SO_4), and concentrated to a brown solid (19.3 g, 61%), which was used directly in the next step without further purification: ^1H NMR δ 2.50 (s, 3H), 4.59 (d, J = 156 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 7.90 (d, J = 8.1 Hz, 2H); ^{13}C NMR δ 21.8, 61.1 (^{13}C), 129.4, 130.3, 146.9.

*p-Toluenesulfonylmethyl (^{13}C)Isocyanide (**TosMIC-$^{13}C^{NC}$**).* The above procedure with paraformaldehyde (3.66 g, 122 mmol), (^{13}C)formamide (5.00 g, 109 mmol), K_2CO_3 (1.52 g, 11.0 mmol), formic acid (28.1 g, 611 mmol), and sodium *p*-toluenesulfinate hydrate (31.5 g, 122 mmol) afforded the title compound as a brown solid (9.20 g, 43%), which was used directly in the next step without further purification: ^1H NMR δ 2.50 (s, 3H), 4.58−4.59 (m, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 21.8, 129.4, 130.4, 131.9, 146.9, 166.0 (^{13}C).

*3-Benzenesulfonyl(5-^{13}C)pyrrole (**9-$^{13}C^5$**).* Following a standard procedure,[63] phenyl vinyl sulfone (16.5 g, 98.5 mmol) and **TosMIC-$^{13}C^{\alpha}$** (19.3 g, 98.5 mmol) in THF/DMSO (450 mL, 2/1)

dx.doi.org/10.1021/jo402488n | J. Org. Chem. 2014, 79, 1001−1016

were added via a cannula to a suspension of NaH (7.9 g, 60% in oil suspension, 0.20 mol) in 150 mL of THF. The reaction mixture was stirred at room temperature for 5 h. Water was added slowly, and the mixture was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and concentrated. Column chromatography (silica, hexanes/ethyl acetate (2/3)) afforded a pale yellow solid (6.07 g, 30%): mp 137−140 °C; ^{1}H NMR δ 6.51−6.54 (m, 1H), 6.79−6.81 (dm, J = 189 Hz, 1H), 7.41−7.43 (m, 1H), 7.46−7.55 (m, 3H), 7.93−7.96 (m, 2H), 8.73 (br s, 1H); ^{13}C NMR δ 108.6 (d, J = 67.9 Hz), 120.1 (^{13}C), 126.8, 129.0, 132.5; ESI-MS obsd 209.0470, calcd 209.0466 [(M + H)$^+$, M = $C_9{}^{13}CH_9NO_2S$].

*3-Benzenesulfonyl(2-^{13}C)pyrrole (**9-^{13}C^2**).* The above procedure with **TosMIC-^{13}C^{NC}** (8.61 g, 43.9 mmol) afforded the title compound as a brown solid (3.82 g, 42%): mp 145−147 °C; ^{1}H NMR δ 6.51−6.54 (m, 1H), 6.78−6.82 (m, 1H), 7.41−7.43 (dm, J = 193 Hz, 1H), 7.46−7.55 (m, 3H), 7.93−7.96 (m, 2H), 8.73 (br s, 1H); ^{13}C NMR δ 108.6 (d, J = 3.8 Hz), 120.2 (d, J = 4.6 Hz), 122.4 (^{13}C), 125.4, 126.8, 129.0, 132.5; ESI-MS obsd 209.0457, calcd 209.0466 [(M + H)$^+$, M = $C_9{}^{13}CH_9NO_2S$].

*4-Benzenesulfonyl-2-formylpyrrole (**10-NA**).* Following a standard procedure,[34] a solution of **9-NA** (8.56 g, 41.4 mmol) in DMF (190 mL) was treated with $POCl_3$ (6.0 mL, 64 mmol). The resulting mixture was stirred at 80 °C for 40 h, cooled to room temperature, treated with a mixture of saturated aqueous sodium acetate and CH_2Cl_2 (400 mL, 1/1), and then stirred for 1 h. The aqueous phase was separated and extracted with CH_2Cl_2. The combined organic extract was washed with saturated brine, dried (Na_2SO_4), and concentrated. Column chromatography (silica, CH_2Cl_2/ethyl acetate (3/2)) afforded a yellow solid (8.58 g, 88%): mp 152−155 °C; ^{1}H NMR δ 7.25 (d, J = 1.5 Hz, 1H), 7.50−7.61 (m, 3H), 7.66 (br s, 1H), 7.95−7.98 (m, 2H), 9.55 (d, J = 1.1 Hz, 1H), 10.1 (br s, 1H); ^{13}C NMR δ 118.9, 127.0, 127.84, 128.29, 129.3, 133.2, 133.5, 142.3, 179.8; ESI-MS obsd 236.0380, calcd 236.0381 [(M + H)$^+$, M = $C_{11}H_9NO_3S$].

*4-Benzenesulfonyl-2-formyl(2-^{13}C)pyrrole (**10-^{13}C^2**).* The above procedure with **9-^{13}C^5** (6.07 g, 29.3 mmol) afforded the title compound as a yellow solid (5.33 g, 77%): mp 157−159 °C; ^{1}H NMR δ 7.25 (br s, 1H), 7.51−7.61 (m, 3H), 7.67 (d, J = 7.0 Hz, 1H), 7.95−7.98 (m, 2H), 9.54 (d, J = 30.4 Hz, 1H), 10.2 (br s, 1H); ^{13}C NMR δ 118.9 (d, J = 65.6 Hz), 127.0, 127.8 (d, J = 5.3 Hz), 128.3, 129.3, 133.2 (d, J = 3.8 Hz), 133.5 (^{13}C), 142.3, 179.8 (d, J = 63.3 Hz); ESI-MS obsd 237.0413, calcd 237.0409 [(M + H)$^+$, M = $C_{10}{}^{13}CH_9NO_3S$].

*4-Benzenesulfonyl-2-formyl(5-^{13}C)pyrrole (**10-^{13}C^5**).* The above procedure with **9-^{13}C^2** (5.84 g, 28.1 mmol) afforded the title compound as a yellow solid (5.17 g, 78%): mp 151−155 °C; ^{1}H NMR δ 7.25−7.28 (m, 1H), 7.51−7.62 (m, 3H), 7.67−7.68 (dm, J = 194 Hz, 1H), 7.95−7.98 (m, 2H), 9.54 (s, 1H), 10.2 (br s, 1H); ^{13}C NMR δ 119.0, 127.0, 127.95 (^{13}C), 129.3, 133.2, 142.3, 179.8 (d, J = 2.3 Hz); ESI-MS obsd 259.0230, calcd 259.0229 [(M + Na)$^+$, M = $C_{10}{}^{13}CH_9NO_3S$].

*tert-Butyl 4-Benzenesulfonyl-2-(1,3-dioxolan-2-yl)pyrrole-1-carboxylate (**11-NA**).* Following standard procedures,[64,65] a solution of **10-NA** (8.58 g, 36.5 mmol) in THF (230 mL) was slowly treated with NaH (1.75 g, 43.8 mmol, 60% in oil suspension) at room temperature under argon. After 1 h, Boc anhydride (8.30 g, 40.0 mmol) was added. The mixture was stirred for 24 h at room temperature, then quenched by the addition of saturated aqueous NH_4Cl, and then extracted with ethyl acetate. The organic extract was concentrated to a dark red oil. The crude solid material was dissolved in benzene (730 mL) and then treated with ethylene glycol (50.8 mL, 91.1 mmol) and p-TsOH·H_2O (0.83 g, 44 mmol). The reaction mixture was refluxed using a Dean−Stark apparatus for 1.5 h. After the mixture was cooled to room temperature, saturated aqueous $NaHCO_3$ (400 mL) was added, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with saturated brine, dried (Na_2SO_4), and concentrated. Recrystallization from hot 2-propanol afforded a brown solid (7.86 g, 57%). The mother liquor was chromatographed (silica, CH_2Cl_2/ethyl acetate (4/1)) to obtain an additional 2.30 g of pale yellow product for a total of 10.16 g (73%): mp 135−137 °C; ^{1}H NMR δ 1.61 (s, 9H), 3.97−4.01 (m, 4H), 6.35 (s, 1H), 6.63−6.64 (m, 1H), 7.49−7.60 (m, 3H), 7.84 (d, J = 1.83 Hz, 1H), 7.94−7.97 (m, 2 H); ^{13}C NMR δ 27.8, 65.0, 86.6, 97.6, 110.3, 125.9, 126.65, 127.18, 129.2, 133.0, 134.7, 142.0, 147.4; ESI-MS obsd 402.0990, calcd 402.0987 [(M + Na)$^+$, M = $C_{18}H_{21}NO_6S$].

*tert-Butyl 4-Benzenesulfonyl-2-(1,3-dioxolan-2-yl)(2-^{13}C)pyrrole-1-carboxylate (**11-^{13}C^2**).* The above procedure with **10-^{13}C^2** (5.33 g, 22.6 mmol) afforded the title compound as a yellow solid (6.60 g, 77%): mp 142−144 °C; ^{1}H NMR δ 1.61 (s, 9H), 3.97−4.01 (m, 4H), 6.35 (d, J = 2.2 Hz, 1H), 6.62−6.64 (m, 1H), 7.49−7.60 (m, 3H), 7.84 (dd, J = 5.3 Hz, J = 2.0 Hz, 1H), 7.94−7.97 (m, 2 H); ^{13}C NMR δ 27.8, 65.0, 86.6, 97.6 (d, J = 65.6 Hz), 110.3 (d, J = 71.7 Hz), 125.9 (d, J = 6.1 Hz), 127.2, 129.2, 133.0, 134.7 (^{13}C), 142.0; ESI-MS obsd 403.1022, calcd 403.1016 [(M + Na)$^+$, M = $C_{17}{}^{13}CH_{21}NO_6S$].

*tert-Butyl 4-Benzenesulfonyl-2-(1,3-dioxolan-2-yl)(5-^{13}C)pyrrole-1-carboxylate (**11-^{13}C^5**).* The above procedure with **10-^{13}C^5** (4.20 g, 17.8 mmol) afforded the title compound as a yellow solid (4.73 g, 70%): mp 129−133 °C; ^{1}H NMR δ 1.61 (s, 9H), 3.97−4.01 (m, 4H), 6.35 (s, 1H), 6.62−6.64 (m, 1H), 7.49−7.60 (m, 3H), 7.83 (dd, J = 98.6 Hz, J = 1.8 Hz, 1H), 7.94−7.97 (m, 2 H); ^{13}C NMR δ 27.8, 65.0, 86.6, 97.5, 110.3, 125.9 (^{13}C), 127.2, 129.2, 133.0, 142.0; ESI-MS obsd 403.1013, calcd 403.1016 [(M + Na)$^+$, M = $C_{17}{}^{13}CH_{21}NO_6S$].

*tert-Butyl 2-(1,3-Dioxolan-2-yl)pyrrole-1-carboxylate (**12-NA**).* Raney nickel (∼100 g, slurry in H_2O) was washed with deionized water (3 × 300 mL) and acetone (3 × 300 mL) before being poured into a three-necked, 1 L flask equipped with a mechanical stirrer and a condenser. A total of 150 mL of acetone was used to facilitate the transfer of Raney nickel into the flask. The Raney nickel−acetone mixture was deactivated at 50 °C with stirring for 2 h before the addition of a solution of **11-NA** (2.28 g, 6.00 mmol) in acetone (50 mL). The mixture was stirred at 50 °C for a further 18 h. The reaction mixture was filtered through a pad of Celite. The filter cake was washed with acetone. The filtrate was concentrated and chromatographed (silica, hexanes/ethyl acetate (3/1)) to yield a colorless liquid (648 mg, 44%): ^{1}H NMR δ 1.60 (s, 9H), 3.97−4.06 (m, 4H), 6.13 (t, J = 3.3 Hz, 1H), 6.41−6.43 (m, 1H), 6.45 (s, 1H), 7.24 (dd, J = 3.3 Hz, J = 1.8 Hz, 1H); ^{13}C NMR δ 27.9, 64.8, 84.2, 98.4, 109.9, 112.5, 122.6, 132.0; ESI-MS obsd 262.1043, calcd 262.1050 [(M + Na)$^+$, M = $C_{12}H_{17}NO_4$].

*tert-Butyl 2-(1,3-Dioxolan-2-yl)(2-^{13}C)pyrrole-1-carboxylate (**12-^{13}C^2**).* Following the above procedure, Raney nickel (∼150 g slurry in H_2O) was deactivated in acetone (450 mL) for 3.5 h before **11-^{13}C^2** (6.60 g, 17.4 mmol) in acetone (50 mL) was added. The mixture was stirred and heated at 50 °C for a further 20 h. Chromatography yielded the title compound as a colorless liquid (1.81 g, 43%). Further elution also recovered starting material **11-^{13}C^2** (1.65 g, 25%), which was combined with another batch and converted to the title compound (average overall yield of 56%): ^{1}H NMR δ 1.60 (s, 9H), 3.97−4.07 (m, 4H), 6.13 (dt, J = 6.6 Hz, J = 3.3 Hz, 1H), 6.41−6.44 (m, 1H), 6.45 (s, 1H), 7.23−7.26 (m, 1H); ^{13}C NMR δ 27.9, 64.8, 98.4 (d, J = 66.4 Hz), 109.9, 112.5 (d, J = 71.0 Hz), 122.7, 132.0 (^{13}C); ESI-MS obsd 263.1085, calcd 263.1083 [(M + Na)$^+$, M = $C_{11}{}^{13}CH_{17}NO_4$].

*tert-Butyl 2-(1,3-Dioxolan-2-yl)(5-^{13}C)pyrrole-1-carboxylate (**12-^{13}C^5**).* The above procedure with **11-^{13}C^5** (4.15 g, 10.9 mmol) afforded the title compound as a yellow solid (1.78 g, 68%): ^{1}H NMR δ 1.60 (s, 9H), 3.97−4.07 (m, 4H), 6.12 (dt, J = 8.7 Hz, J = 3.3 Hz, 1H), 6.40−6.44 (m, 1H), 6.45 (s, 1H), 7.24−7.25 (dm, J = 192.0 Hz, 1H); ^{13}C NMR δ 27.9, 64.8, 98.4, 112.5, 122.6 (^{13}C) ; ESI-MS obsd 263.1077, calcd 263.1083 [(M + Na)$^+$, M = $C_{11}{}^{13}CH_{17}NO_4$].

*(2-^{13}C)Pyrrole-2-carboxaldehyde (**5-^{13}C^2**).* Following a standard procedure,[73] **12-^{13}C^2** (2.45 g, 10.2 mmol) in a 50 mL flask was treated with AcOH/H_2O (24 mL, 1/1). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched by the slow addition of saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4) and concentrated. The residue was dissolved in freshly distilled THF (40 mL) and treated with NaOMe (1.95 g, 36.1 mmol) in MeOH (6 mL). The reaction mixture was stirred for 15 min and then treated with water and diethyl ether. The organic extract was dried (Na_2SO_4) and concentrated to yield a brown solid (760 mg, 78%): mp 35−37 °C; ^{1}H

dx.doi.org/10.1021/jo402488n | J. Org. Chem. 2014, 79, 1001−1016

NMR δ 6.34−6.38 (m, 1H), 6.97−7.01 (m, 1H), 7.12−7.14 (m, 1H), 9.31 (br s, 1H), 9.53 (d, J = 29.0 Hz, 1H); ^{13}C NMR δ 111.3 (d, J = 2.3 Hz), 120.1, 132.9 (^{13}C), 179.2 (d, J = 65.6 Hz); ESI-MS obsd 97.0483, calcd 97.0478 [(M + H)$^+$, M = $C_4{}^{13}CH_5NO$].

*(5-^{13}C)Pyrrole-2-carboxaldehyde (**5-^{13}C^5**).* The above procedure with **12-^{13}C^5** (3.45 g, 14.4 mmol) afforded the title compound as a brown solid (1.13 g, 82%): mp 33−37 °C; ^{1}H NMR δ 6.35−6.38 (m, 1H), 6.98−7.02 (m, 1H), 7.15 (d, J = 186 Hz, 1H), 9.52 (s, 1H), 9.85 (br s, 1H); ^{13}C NMR δ 111.3 (d, J = 62.6 Hz), 126.4 (^{13}C), 179.3; ESI-MS obsd 97.0481, calcd 97.0478 [(M + H)$^+$, M = $C_4{}^{13}CH_5NO$].

Nitroethylpyrroles {3}. *2-(2-Nitroethyl)(**^{15}N^{pyrrol}**)pyrrole (**3-^{15}N^{pyrrol}**).* Following a standard procedure[34] with slight modification (procedure A), a mixture of **5-^{15}N** (1.73 g, 18.0 mmol), potassium acetate (1.40 g, 14.3 mmol), and methylamine hydrochloride (0.97 g, 14 mmol) in absolute ethanol (6.3 mL) was treated with nitromethane (2.5 mL, 47 mmol) with stirring. The mixture was stirred for 2.5 h, whereupon water was added. The mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated to yield a dark yellow solid. The crude solid material was dissolved in freshly distilled THF (81 mL), and the solution was cooled to −10 °C. The solution was treated with $LiBH_4$ (0.48 g, 90%, 22 mmol) all at once with vigorous stirring. The reaction mixture was stirred for 25 min at −10 °C, whereupon the reaction mixture was quenched by slow addition of 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. Column chromatography (silica, hexanes/ethyl acetate (3/1)) afforded an orange oil (1.07 g, 42%): ^{1}H NMR δ 3.31 (td, J = 6.8 Hz, J = 2.2 Hz, 2H), 4.60 (t, J = 6.8 Hz, 2H), 6.00−6.02 (m, 1H), 6.13−6.16 (m, 1H), 6.70−6.72 (m, 1H), 8.17 (dq, J = 95.3 Hz, J = 2.6 Hz, 1H); ^{13}C NMR δ 25.5, 75.4, 106.9 (d, J = 5.3 Hz), 108.8 (d, J = 3.1 Hz), 117.8 (d, J = 13.0 Hz), 126.0; ^{15}N NMR δ −228.1; ESI-MS obsd 140.0479, calcd 140.0483 [(M − H)$^-$, M = $C_6H_8N^{15}NO_2$].

*2-[2-(**^{15}N)Nitroethyl]pyrrole (**3-^{15}N^{nitro}**).* Procedure A with **5-NA** (1.74 g, 18.3 mmol) and $CH_3{}^{15}NO_2$ (1.00 g, 16.1 mmol) afforded the title compound as an orange oil (863 mg, 38%): ^{1}H NMR δ 3.31 (td, J = 6.7 Hz, J = 3.5 Hz, 2H), 4.60 (td, J = 6.7 Hz, J = 2.3 Hz, 2H), 6.00−6.02 (m, 1H), 6.13−6.16 (m, 1H), 6.70−6.72 (m, 1H), 8.17 (br s, 1H); ^{13}C NMR δ 25.5 (^{13}C), 75.3 (d, J = 7.6 Hz), 106.9, 108.8, 117.8, 126.0; ^{15}N NMR δ 5.9; ESI-MS obsd 142.0630, calcd 142.0629 [(M + H)$^+$, M = $C_6H_8N^{15}NO_2$].

*2-[2-Nitro(1-^{13}C)ethyl]pyrrole (**3-^{13}C^1**).* Procedure A with **5-^{13}C^{formyl}** (1.01 g, 10.5 mmol) afforded the title compound as an orange oil (513 mg, 35%): ^{1}H NMR δ 3.31 (dt, J = 131 Hz, J = 6.7 Hz, 2H), 4.60 (td, J = 6.7 Hz, J = 3.3 Hz, 2H), 6.01 (br s, 1H), 6.13−6.16 (m, 1H), 6.71 (br s, 1H), 8.17 (br s, 1H); ^{13}C NMR δ 25.4, 75.3 (d, J = 35.9 Hz), 106.9 (d, J = 3.8 Hz), 108.8 (d, J = 3.1 Hz), 117.8, 126.0 (d, J = 52.6 Hz); ESI-MS obsd 142.0690, calcd 142.0692 [(M + H)$^+$, M = $C_5{}^{13}CH_8N_2O_2$].

*2-[2-Nitro(2-^{13}C)ethyl]pyrrole (**3-^{13}C^2**).*[78] Procedure A with **5-NA** (2.72 g, 28.6 mmol) and $^{13}CH_3NO_2$ (1.77 g, 28.5 mmol) afforded the title compound as an orange oil (1.41 g, 35%): ^{1}H NMR δ 3.31 (td, J = 6.7 Hz, J = 4.9 Hz, 2H), 4.60 (dt, J = 147 Hz, J = 6.7 Hz, 2H), 6.01 (br s, 1H), 6.13−6.16 (m, 1H), 6.71−6.72 (m, 1H), 8.17 (br s, 1H); ^{13}C NMR δ 75.3 (^{13}C); ESI-MS obsd 140.0551, calcd 140.0547 [(M − H)$^-$, M = $C_5{}^{13}CH_8N_2O_2$].

*2-(2-Nitroethyl)(2-^{13}C)pyrrole (**3-^{13}C$^{\alpha}$**).* Following a standard procedure (procedure B),[43] **5-^{13}C^2** (1.76 g, 18.3 mmol) was dissolved in methanol (55 mL) and treated with nitromethane (2.96 mL, 55.2 mmol), sodium acetate (1.66 g, 20.0 mmol), and methylamine hydrochloride (1.66 g, 20.0 mmol). Stirring at room temperature for 12 h afforded a yellow-brown mixture. DMF (37 mL) and methanol (31 mL) were added to the reaction mixture. $NaBH_4$ (2.43 g, 63.9 mmol) was added portionwise. The reaction mixture was stirred at room temperature for 1 h, neutralized with acetic acid (∼3 mL), and concentrated. The mixture was dissolved in CH_2Cl_2 and washed with water. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed (silica, hexanes/ethyl acetate (3/1)) to give an orange oil (1.70 g, 66%): ^{1}H NMR δ 3.32 (td, J = 6.6 Hz, J = 6.6 Hz, 2H), 4.60 (dt, J = 6.6 Hz, J = 4.4 Hz, 2H), 5.99−6.03 (m, 1H), 6.12−6.17 (m, 1H), 6.70−6.73 (m, 1H), 8.17 (br s, 1H); ^{13}C NMR δ 25.4 (d, J = 52.6 Hz), 75.3, 106.9 (d, J = 68.7 Hz), 108.8 (d, J = 2.3 Hz), 117.8 (d, J = 7.6 Hz), 126.0; ESI-MS obsd 142.0693, calcd 142.0692 [(M + H)$^+$, M = $C_5{}^{13}CH_8N_2O_2$].

*2-(2-Nitroethyl)(5-^{13}C)pyrrole (**3-^{13}C$^{\gamma}$**).* Procedure B with **5-^{13}C^5** (1.60 g, 16.7 mmol) afforded the title compound as an orange oil (1.62 g, 69%): ^{1}H NMR δ 3.31 (t, J = 6.8 Hz, 2H), 4.60 (t, J = 6.8 Hz, 2H), 6.00−6.03 (m, 1H), 6.13−6.17 (m, 1H), 6.71−6.72 (dm, J = 185 Hz, 1H), 8.17 (br s, 1H); ^{13}C NMR δ 25.4, 75.3, 106.9, 108.8 (d, J = 66.4 Hz), 117.8 (^{13}C), 126.0; ESI-MS obsd 142.0694, calcd 142.0692 [(M + H)$^+$, M = $C_5{}^{13}CH_8N_2O_2$].

α,β-Unsaturated Ketone−Acetals {4}. *1,1-Dimethoxy-4-methyl-3-(2-^{13}C)penten-2-one (**4-^{13}C^2**).* Following a standard procedure,[77] a round-bottom flask equipped with a 10 cm Vigreux column and a short-path condenser was charged with bis(trimethylsilyl) sulfate (11.5 g, 47.2 mmol) and K^{13}CN (4.30 g, 65.2 mmol). The reaction mixture was heated and distilled at 200 °C. The distillate was collected (40−60 °C at top of column) as a colorless liquid and found (by ^{1}H NMR spectroscopy) to contain TMS^{13}CN (∼2.48 g, ∼38%) and silyl-containing species. The crude distillate was used without further purification: ^{1}H NMR δ 0.37 (d, J = 2.9 Hz). Following a standard procedure,[40] the crude distillate (containing ∼2.48 g of TMS^{13}CN, 24.8 mmol) was combined with trimethyl orthoformate (5.39 mL, 49.2 mmol) and treated dropwise with $BF_3{\cdot}OEt_2$ (0.50 mL, 4.0 mmol) under argon at room temperature. The reaction mixture was stirred for 3 h at room temperature, whereupon saturated aqueous $NaHCO_3$ was added. The aqueous phase was extracted with diethyl ether. The organic phase was washed with saturated brine, dried (Na_2SO_4), and concentrated. The residue was treated dropwise with **6** (123 mL, 61.5 mmol, 0.5 M in THF) under argon at 0 °C, followed by stirring for 2 h at room temperature. The reaction mixture was treated with saturated aqueous NH_4Cl (500 mL) and vigorously stirred for 3 h. The aqueous phase was extracted with diethyl ether. The organic phase was washed with saturated brine, dried (Na_2SO_4), and concentrated. The resulting mixture was chromatographed (silica, hexanes/ethyl acetate (3/1)) to afford a pale yellow liquid (2.02 g, 19% from K^{13}CN): ^{1}H NMR δ 1.96 (s, 3H), 2.21 (s, 3H), 3.42 (s, 6H), 4.49 (s, 1H), 6.36−6.38 (m, 1H); ^{13}C NMR δ 21.3 (d, J = 1.5 Hz), 28.1 (d, J = 6.1 Hz), 54.5 (d, J = 2.3 Hz), 104.5 (d, J = 53.4 Hz), 119.0 (d, J = 56.5 Hz), 160.2, 194.1 (^{13}C); ESI-MS obsd 182.0866, calcd 182.0869 [(M + Na)$^+$, M = $C_7{}^{13}CH_{14}O_3$].

*1,1-Diethoxy-4-methyl-3-(1-^{13}C)penten-2-one (**4Et-^{13}C^1**).* Following a standard procedure,[40] a mixture of TMSCN (1.25 mL, 1.70 mmol) and triethyl (^{13}C)orthoformate (1.50 g, 10.5 mmol) in a round-bottom flask was treated dropwise with $BF_3{\cdot}OEt_2$ (0.2 mL, 0.1 mmol) under argon at room temperature. The reaction mixture was stirred for 3 h at room temperature, whereupon a solution of saturated aqueous $NaHCO_3$ was added. The aqueous phase was extracted with diethyl ether. The organic phase was washed with saturated brine, dried (Na_2SO_4), and concentrated. The residue was treated dropwise under argon with **6** (32 mL, 16 mmol, 0.5 M in THF) at 0 °C, followed by stirring for 2 h at room temperature. The reaction mixture was treated with saturated aqueous NH_4Cl (150 mL) and vigorously stirred for 3 h. The aqueous phase was extracted with diethyl ether. The organic phase was washed with saturated brine, dried (Na_2SO_4), and concentrated. The resulting mixture was chromatographed (silica, hexanes/ethyl acetate (3/1)) to afford a pale yellow liquid (742 mg, 38%): ^{1}H NMR δ 1.25 (t, J = 7.1 Hz, 6H), 1.95 (d, J = 1.1 Hz, 3H), 2.20 (d, J = 1.1 Hz, 3H), 3.54−3.74 (m, 4H), 4.58 (d, J = 161 Hz 1H), 6.40−6.41 (m, 1H); ^{13}C NMR δ 15.1 (d, J = 3.1 Hz), 21.2, 28.1, 62.9, 103.1 (^{13}C), 119.0 (d, J = 13.7 Hz), 159.8, 194.7 (d, J = 54.2 Hz); ESI-MS obsd 210.1176, calcd 210.1182 [(M + Na)$^+$, M = $C_9{}^{13}CH_{18}O_3$].

Nitrohexanone−Pyrroles 2. *1,1-Dimethoxy-4,4-dimethyl-5-nitro-6-[2-(1-^{15}N)pyrrolyl]-2-hexanone (**2-^{15}N^{pyrrol}**).* Following a standard procedure[41] with slight modification, a mixture of **3-^{15}N^{pyrrol}** (1.04 g, 7.38 mmol) and **4-NA** (2.33 g, 14.8 mmol) was treated with DBU (3.3 mL, 22 mmol). Ethyl acetate (∼2 mL) was added as required to completely dissolve the reaction mixture. The reaction mixture was stirred at room temperature for 16 h, diluted with ethyl acetate, and washed with saturated aqueous NH_4Cl solution and brine.

dx.doi.org/10.1021/jo402488n | J. Org. Chem. 2014, 79, 1001−1016

The organic layer was dried (Na_2SO_4) and concentrated. The resulting mixture was chromatographed (silica, hexanes/ethyl acetate (3/1)) to afford a brown solid (1.95 mg, 88%): mp 65−68 °C; ^{1}H NMR δ 1.14 (s, 3H), 1.23 (s, 3H), 2.55, 2.77 (AB, ^2J = 18.5 Hz, 2H), 3.01−3.06 (m, 1H), 3.30−3.39 (m, 1H), 3.43 (s, 3H), 3.44 (s, 3H), 4.36 (s, 1H), 5.15 (ABX, ^3J = 2.2 Hz, ^3J = 11.7 Hz, 1H), 5.97−5.99 (m, 1H), 6.08−6.11 (m, 1H), 6.65−6.67 (m, 1H), 8.08 (dm, J = 95.1 Hz, 1H); ^{13}C NMR δ 24.17, 24.26, 26.6 (d, J = 2.3 Hz), 36.4, 45.0, 55.1, 94.7, 104.6, 107.2 (d, J = 4.6 Hz), 108.6 (d, J = 3.8 Hz), 117.7 (d, J = 13.7 Hz), 125.9 (d, J = 13.7 Hz), 203.6; ^{15}N NMR δ −227.8; ESI-MS obsd 322.1398, calcd 322.1391 [(M + Na)$^+$, M = $C_{14}H_{22}N^{15}NO_5$].

*1,1-Dimethoxy-4,4-dimethyl-5-(^{15}N)nitro-6-(2-pyrrolyl)-2-hexanone (**2-^{15}N^{nitro}**).* The above procedure with **3-^{15}N^{nitro}** (863 mg, 6.12 mmol) afforded the title compound as a brown solid (1.43 g, 78%): mp 73−74 °C; ^{1}H NMR δ 1.14 (s, 3H), 1.23 (s, 3H), 2.55, 2.77 (AB, ^2J = 18.5 Hz, 2H), 3.03 (ABX, ^3J = 2.6 Hz, ^2J = 15.4 Hz, 1H, $^3J_{NH}$ = 6.6 Hz), 3.36 (ABX, ^3J = 11.7 Hz, ^2J = 15.4 Hz, 1H, $^3J_{NH}$ = 1.6 Hz), 3.43 (s, 3H), 3.44 (s, 3H), 4.36 (s, 1H), 5.15 (ABX, ^3J = 2.6 Hz, ^3J = 11.7 Hz, 1H, $^2J_{NH}$ = 1.2 Hz), 5.97−5.99 (m, 1H), 6.08−6.11 (m, 1H), 6.65−6.67 (m, 1H), 8.08 (br s, 1H); ^{13}C NMR δ 24.18, 24.28, 26.6, 36.4, 45.0, 55.2, 94.8 (d, J = 5.3 Hz), 104.7, 107.2, 108.7, 117.7, 125.9, 203.6; ^{15}N NMR δ 10.3; ESI-MS obsd 300.1572, calcd 300.1567 [(M + H)$^+$, M = $C_{14}H_{22}N^{15}NO_5$].

*1,1-Dimethoxy-4,4-dimethyl-5-nitro-6-(2-pyrrolyl)-2-(6-^{13}C)-hexanone (**2-^{13}C^6**).* The above procedure with **3-^{13}C^1** (764 mg, 5.42 mmol) afforded the title compound as a brown solid (1.36 g, 84%): mp 70−72 °C; ^{1}H NMR δ 1.14 (s, 3H), 1.23 (s, 3H), 2.55, 2.77 (AB, ^2J = 18.5 Hz, 2H), 3.03 (ABX, ^3J = 2.6 Hz, ^2J = 15.4 Hz, 1H, $^1J_{CH}$ = 128 Hz), 3.36 (ABX, ^3J = 11.7 Hz, ^2J = 15.4 Hz, 1H, $^1J_{CH}$ = 131 Hz), 3.43 (s, 3H), 3.44 (s, 3H), 4.36 (s, 1H), 5.15 (ABX, ^3J = 2.6 Hz, ^3J = 11.7 Hz, 1H, $^3J_{CH}$ = 2.6 Hz), 5.97−5.99 (m, 1H), 6.08−6.11 (m, 1H), 6.65−6.67 (m, 1H), 8.08 (br s, 1H); ^{13}C NMR δ 24.10, 24.18, 26.6 (^{13}C), 36.3, 45.0, 55.1, 94.7 (d, J = 37.4 Hz), 104.5, 107.1 (d, J = 3.8 Hz), 108.6 (d, J = 3.1 Hz), 117.6, 125.9 (d, J = 51.9 Hz), 203.6; ESI-MS obsd 322.1457, calcd 322.1454 [(M + Na)$^+$, M = $C_{13}{}^{13}CH_{22}N_2O_5$].

*1,1-Dimethoxy-4,4-dimethyl-5-nitro-6-(2-pyrrolyl)-2-(5-^{13}C)-hexanone (**2-^{13}C^5**).* The above procedure with **3-^{13}C^2** (1.41 g, 10.0 mmol) afforded the title compound as a brown solid (2.48 g, 83%): mp 71−73 °C; ^{1}H NMR δ 1.14 (d, J = 4.0 Hz, 3H), 1.23 (d, J = 4.0 Hz, 3H), 2.55, 2.77 (AB, ^2J = 18.5 Hz, $^3J_{CH}$ = 3.8 Hz, 2H), 3.03 (m, 1H), 3.36 (ABX, ^3J = 11.7 Hz, ^2J = 15.4 Hz, 1H, $^2J_{CH}$ = 7.0 Hz), 3.43 (s, 3H), 3.44 (s, 3H), 4.36 (s, 1H), 5.15 (ABX, ^3J = 2.6 Hz, ^3J = 11.7 Hz, 1H, $^1J_{CH}$ = 151 Hz), 5.97−5.99 (m, 1H), 6.08−6.11 (m, 1H), 6.65−6.67 (m, 1H), 8.08 (br s, 1H); ^{13}C NMR δ 24.16, 24.26, 26.6 (d, J = 36.6 Hz), 36.4 (d, J = 32.8 Hz), 45.0, 55.1, 94.8 (^{13}C), 104.6, 107.2, 108.6, 117.7, 125.9, 203.6; ESI-MS obsd 322.1444, calcd 322.1454 [(M + Na)$^+$, M = $C_{13}{}^{13}CH_{22}N_2O_5$].

*1,1-Dimethoxy-4,4-dimethyl-5-nitro-6-(2-pyrrolyl)-2-(2-^{13}C)-hexanone (**2-^{13}C^2**).* The above procedure with **3-NA** (1.29 g, 9.21 mmol) and **4-^{13}C^2** (1.22 g, 7.67 mmol) afforded the title compound as a brown solid (1.50 g, 65%): mp 66−68 °C; ^{1}H NMR δ 1.14 (s, 3H), 1.23 (s, 3H), 2.55, 2.77 (AB, ^2J = 18.5 Hz, 2H, $^2J_{CH}$ = 6.0 Hz), 3.03 (ABX, ^3J = 2.6 Hz, ^2J = 15.4 Hz, 1H), 3.36 (ABX, ^3J = 11.7 Hz, ^2J = 15.4 Hz, 1H), 3.43 (s, 3H), 3.44 (s, 3H), 4.36 (s, 1H), 5.15 (ABX, ^3J = 2.6 Hz, ^3J = 11.7 Hz, 1H), 5.97−5.99 (m, 1H), 6.08−6.11 (m, 1H), 6.65−6.67 (m, 1H), 8.08 (br s, 1H); ^{13}C NMR δ 24.04 (d, J = 1.5 Hz), 24.12, (d, J = 2.3 Hz), 26.6, 36.3, (d, J = 1.5 Hz), 44.9, (d, J = 39.7 Hz), 55.0, (d, J = 3.1 Hz), 94.7, 104.5 (d, J = 53.4 Hz), 107.0, 108.5, 117.6, 125.9, 203.6 (^{13}C); ESI-MS obsd 300.1630, calcd 300.1635 [(M + H)$^+$, M = $C_{13}{}^{13}CH_{22}N_2O_5$].

*1,1-Dimethoxy-4,4-dimethyl-5-nitro-6-[2-(2-^{13}C)pyrrolyl]-2-hexanone (**2-^{13}C$^\alpha$**).* The above procedure with **3-^{13}C$^\alpha$** (1.70 g, 12.1 mmol) afforded the title compound as a brown solid (3.26 g, 91%): mp 70−72 °C; ^{1}H NMR δ 1.14 (s, 3H), 1.23 (s, 3H), 2.55, 2.77 (AB, ^2J = 18.5 Hz, 2H), 3.03 (ABX, ^3J = 2.6 Hz, ^2J = 15.5 Hz, 1H, $^2J_{CH}$ = 7.1 Hz), 3.36 (m, 1H), 3.43 (s, 3H), 3.44 (s, 3H), 4.36 (s, 1H), 5.15 (ABX, ^3J = 2.6 Hz, ^3J = 11.7 Hz, 1H, $^3J_{CH}$ = 2.6 Hz), 5.96−6.00 (m, 1H), 6.08−6.12 (m, 1H), 6.64−6.68 (m, 1H), 8.08 (br s, 1H); ^{13}C NMR δ 24.20, 24.30, 26.6 (d, $^2J_{CC}$ = 52.6 Hz), 36.4, 45.0, 55.2, 94.8, 104.7, 106.9, 108.9 (d, J = 2.3 Hz), 117.7 (d, J = 7.6 Hz), 126.0 (^{13}C), 203.6; ESI-MS obsd 300.1634, calcd 300.1635 [(M + H)$^+$, M = $C_{13}{}^{13}CH_{22}N_2O_5$].

*1,1-Dimethoxy-4,4-dimethyl-5-nitro-6-[2-(5-^{13}C)pyrrolyl]-2-hexanone (**2-^{13}C$^\gamma$**).* The above procedure with **3-^{13}C$^\gamma$** (1.60 g, 11.3 mmol) afforded the title compound as a brown solid (3.20 g, 95%): mp 70−74 °C; ^{1}H NMR δ 1.14 (s, 3H), 1.23 (s, 3H), 2.55, 2.77 (AB, ^2J = 18.5 Hz, 2H), 3.03 (ABX, ^3J = 2.6 Hz, ^2J = 15.5 Hz, 1H), 3.36 (m, 1H), 3.43 (s, 3H), 3.44 (s, 3H), 4.36 (s, 1H), 5.15 (ABX, ^3J = 2.6 Hz, ^3J = 11.7 Hz, 1H), 5.96−6.00 (m, 1H), 6.08−6.12 (m, 1H), 6.64−6.68 (dm, J = 185 Hz, 1H), 8.08 (br s, 1H); ^{13}C NMR δ 24.20, 24.30, 26.6, 36.4, 45.0, 55.2, 94.8, 104.7, 106.9, 117.7 (^{13}C), 203.6; ESI-MS obsd 300.1638, calcd 300.1635 [(M + H)$^+$, M = $C_{13}{}^{13}CH_{22}N_2O_5$].

*1,1-Diethoxy-4,4-dimethyl-5-nitro-6-(2-pyrrolyl)-2-hexanone (**2Et-NA**).* The above procedure with **3-NA** (872 mg, 4.69 mmol) and **4Et-NA** (656 mg, 3.53 mmol) afforded the title compound as a yellow liquid (1.22 g, 80%): ^{1}H NMR δ 1.15 (s, 3H), 1.22 (s, 3H), 1.25 (t, J = 7.0 Hz, 6H), 2.61, 2.78 (AB, ^2J = 18.3 Hz, 2H), 3.04 (ABX, ^3J = 2.2 Hz, ^2J = 15.4 Hz, 1H), 3.36 (ABX, ^3J = 11.7 Hz, ^2J = 15.4 Hz, 1H), 3.54−3.62 (m, 2H), 3.76−3.77 (m, 2H), 4.47 (s, 1H), 5.17 (ABX, ^3J = 2.6 Hz, ^3J = 11.8 Hz, 1H), 5.97−5.99 (m, 1H), 6.08−6.11 (m, 1H), 6.65−6.67 (m, 1H), 8.07 (br s, 1H); ^{13}C NMR δ 15.1, 24.1, 24.4, 26.7, 36.5, 44.6, 63.8, 94.9, 103.2, 107.3, 108.7, 117.7, 204.1; ESI-MS obsd 349.1735, calcd 349.1734 [(M + Na)$^+$, M = $C_{16}H_{26}N_2O_5$].

*1,1-Diethoxy-4,4-dimethyl-5-nitro-6-(2-pyrrolyl)-2-(1-^{13}C)-hexanone (**2Et-^{13}C^1**).* The above procedure with **3-NA** (634 mg, 4.53 mmol) and **4Et-^{13}C^1** (706 mg, 3.78 mmol) afforded the title compound as a yellow liquid (928 mg, 75%): ^{1}H NMR δ 1.15 (s, 3H), 1.22 (s, 3H), 1.25 (t, J = 7.0 Hz, 6H), 2.61, 2.78 (AB, ^2J = 18.3 Hz, 2H), 3.04 (ABX, ^3J = 2.2 Hz, ^2J = 15.4 Hz, 1H), 3.36 (ABX, ^3J = 11.7 Hz, ^2J = 15.4 Hz, 1H), 3.54−3.62 (m, 2H), 3.76−3.77 (m, 2H), 4.47 (d, J = 162 Hz, 1H), 5.17 (ABX, ^3J = 2.6 Hz, ^3J = 11.8 Hz, 1H), 5.97−5.99 (m, 1H), 6.08−6.11 (m, 1H), 6.65−6.67 (m, 1H), 8.07 (br s, 1H); ^{13}C NMR δ 15.1, 24.1, 24.4, 26.7, 36.5, 44.6 (d, J = 11.4 Hz), 63.8, 94.9, 103.2 (^{13}C), 107.3, 108.7, 117.7, 126.0, 204.1 (d, J = 54.2 Hz); ESI-MS obsd 350.1759, calcd 350.1767 [(M + Na)$^+$, M = $C_{15}{}^{13}CH_{26}N_2O_5$].

Dihydrodipyrrin−Acetals 1. *2,3-Dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyl(11-^{15}N)dipyrrin (**1-^{15}N^{11}**).* Following a standard procedure[34] with an increased amount of buffer (see the Supporting Information), a solution of **2-^{15}N^{pyrrol}** (1.95 g, 6.52 mmol) in freshly distilled THF (15 mL) was treated with NaOMe (1.76 g, 32.6 mmol) at 0 °C. The reaction mixture was stirred and degassed with argon for 30 min (first flask). In a second flask, $TiCl_3$ (32.6 mL, 20 wt % $TiCl_3$ in 3% HCl, 55.6 mmol), THF (67 mL), and NH_4OAc (50.2 g, 652 mmol) were combined. The mixture was degassed with argon for 30 min. The mixture in the first flask was transferred via a cannula to the buffered $TiCl_3$ mixture. The resulting mixture was stirred at room temperature for 16 h. Then the mixture was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic extract was washed with water, dried (Na_2SO_4), and concentrated. Chromatography (3 × 30 cm, ∼80 g of neutral alumina, CH_2Cl_2) afforded a dark brown oil (939 mg, 58%): ^{1}H NMR δ 1.21 (s, 6H), 2.61 (s, 2H), 3.45 (s, 6H), 5.02 (s, 1H), 5.88 (d, J = 3.7 Hz, 1H), 6.15−6.16 (m, 2H), 6.83−6.85 (m, 1H), 10.65 (dm, J = 97.3, 1H); ^{13}C NMR δ 29.1, 40.0, 48.1, 54.6, 102.8, 107.4, 108.4 (d, J = 3.1 Hz), 109.1 (d, J = 4.6 Hz), 119.4 (d, J = 13.0 Hz), 130.6 (d, J = 13.7 Hz), 159.2, 173.8; ^{15}N NMR δ −229.0; ESI-MS obsd 272.1385, calcd 272.1387 [(M + Na)$^+$, M = $C_{14}H_{20}N^{15}NO_2$].

*2,3-Dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyl(10-^{15}N)-dipyrrin (**1-^{15}N^{10}**).* The above procedure with **2-^{15}N^{nitro}** (1.43 g, 4.78 mmol) afforded the title compound as a dark brown oil (487 mg, 41%): ^{1}H NMR δ 1.20 (s, 6H), 2.60 (d, J = 2.2 Hz, 2H), 3.44 (s, 6H), 5.01 (s, 1H), 5.87 (d, J = 5.9 Hz 1H), 6.15−6.16 (m, 2H), 6.83−6.85 (m, 1H), 10.65 (br s, 1H); ^{13}C NMR δ 29.0, 39.9, 48.0 (d, J = 1.5 Hz), 54.5, 102.7 (d, J = 9.2 Hz), 107.4 (d, J = 3.8 Hz), 108.4, 109.1, 119.3, 130.5, 159.1 (d, J = 1.5 Hz), 173.7 (d, J = 5.3 Hz); ^{15}N NMR δ −58.3; ESI-MS obsd 272.1390, calcd 272.1387 [(M + Na)$^+$, M = $C_{14}H_{20}N^{15}NO_2$].

*2,3-Dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyl(1-^{13}C)-dipyrrin (**1-^{13}C^1**).* The above procedure with **2-^{13}C^2** (1.50 g, 5.02

dx.doi.org/10.1021/jo402488n | J. Org. Chem. 2014, 79, 1001−1016

mmol) afforded the title compound as a dark brown oil (720 mg, 58%): ^{1}H NMR δ 1.21 (s, 6H), 2.61 (d, J = 6.2 Hz, 2H), 3.45 (s, 6H), 5.01 (s, 1H), 5.88 (s, 1H), 6.15−6.16 (m, 2H), 6.83−6.85 (m, 1H), 10.65 (br s, 1H); ^{13}C NMR δ 29.1, 48.1 (d, J = 35.1 Hz), 54.5, 102.8 (d, J = 64.1 Hz), 107.4 (d, J = 9.9 Hz), 108.5, 109.1, 119.4, 173.8 (^{13}C); ESI-MS obsd 250.1632, calcd 250.1631 [(M + H)$^+$, M = $C_{13}{}^{13}CH_{20}N_2O_2$].

*2,3-Dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyl(4-^{13}C)-dipyrrin (**1-^{13}C^4**).* The above procedure with **2-^{13}C^5** (2.47 g, 8.33 mmol) afforded the title compound as a dark brown oil (1.16 mg, 56%): ^{1}H NMR δ 1.21 (d, J = 4.0 Hz, 6H), 2.61 (s, 2H), 3.45 (s, 6H), 5.01 (s, 1H), 5.88 (s, 1H), 6.15−6.16 (m, 2H), 6.83−6.85 (m, 1H), 10.65 (br s, 1H); ^{13}C NMR δ 29.1, 48.1 (d, J = 4.6 Hz), 54.6, 102.8 (d, J = 9.9 Hz), 107.4 (d, J = 82.4 Hz), 108.5, 109.1 (d, J = 6.1 Hz), 119.4, 159.2 (^{13}C); ESI-MS obsd 250.1631, calcd 250.1631 [(M + H)$^+$, M = $C_{13}{}^{13}CH_{20}N_2O_2$].

*2,3-Dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyl(5-^{13}C)-dipyrrin (**1-^{13}C^5**).* The above procedure with **2-^{13}C^6** (1.69 g, 5.65 mmol) afforded the title compound as a dark brown oil (463 mg, 33%): ^{1}H NMR δ 1.20 (s, 6H), 2.61 (s, 2H), 3.45 (s, 6H), 5.01 (s, 1H), 5.88 (d, J = 153 Hz, 1H), 6.15−6.16 (m, 2H), 6.83−6.85 (m, 1H), 10.64 (br s, 1H); ^{13}C NMR δ 29.1, 40.0 (d, J = 5.3 Hz), 48.1, 54.5, 102.8, 107.4 (^{13}C), 108.4 (d, J = 5.3 Hz), 109.1 (d, J = 4.6 Hz), 119.4, 130.6 (d, J = 66.4 Hz), 159.2 (d, J = 81.6 Hz), 173.8 (d, J = 9.2 Hz); ESI-MS obsd 272.1438, calcd 272.1451 [(M + Na)$^+$, M = $C_{13}{}^{13}CH_{20}N_2O_2$].

*2,3-Dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyl(6-^{13}C)-dipyrrin (**1-^{13}C^6**).* The above procedure with **2-^{13}C$^\alpha$** (1.00 g, 3.34 mmol) afforded the title compound as a dark brown oil (354 mg, 43%): ^{1}H NMR δ 1.21 (s, 6H), 2.61 (s, 2H), 3.45 (s, 6H), 5.01 (s, 1H), 5.87−5.88 (m, 1H), 6.15−6.17 (m, 2H), 6.83−6.85 (m, 1H), 10.65 (br s, 1H); ^{13}C NMR δ 29.1, 40.0, 48.1, 54.5, 102.8, 107.4 (d, J = 66.4 Hz), 108.4, 109.1 (d, J = 67.1 Hz), 119.4 (d, J = 6.9 Hz), 130.6 (^{13}C), 173.8; ESI-MS obsd 250.1628, calcd 250.1631 [(M + H)$^+$, M = $C_{13}{}^{13}CH_{20}N_2O_2$].

*2,3-Dihydro-1-(1,1-dimethoxymethyl)-3,3-dimethyl(9-^{13}C)-dipyrrin (**1-^{13}C^9**).* The above procedure with **2-^{13}C$^\gamma$** (1.50 g, 5.02 mmol) afforded the title compound as a dark brown oil (634 mg, 51%): ^{1}H NMR δ 1.21 (s, 6H), 2.61 (s, 2H), 3.45 (s, 6H), 5.01 (s, 1H), 5.88 (s, 1H), 6.15−6.16 (m, 2H), 6.83−6.85 (dm, J = 184 Hz, 1H), 10.65 (br s, 1H); ^{13}C NMR δ 29.1, 40.0, 48.1, 54.6, 102.8, 107.4, 109.1, 119.4 (^{13}C); ESI-MS obsd 250.1630, calcd 250.1631 [(M + H)$^+$, M = $C_{13}{}^{13}CH_{20}N_2O_2$].

*2,3-Dihydro-1-(1,1-diethoxymethyl)-3,3-dimethyldipyrrin (**1Et-NA**).* The above procedure with **2Et-NA** (928 mg, 2.85 mmol) afforded the title compound as a dark brown oil (256 mg, 32%): ^{1}H NMR δ 1.20 (s, 6H), 1.26 (t, J = 7.1 Hz, 6H), 2.64 (s, 2H), 3.56−3.63 (m, 2H), 3.72−3.80 (m, 2H), 5.15 (s, 1H), 5.87 (s, 1H), 6.14−6.17 (m, 2H), 6.83−6.84 (m, 1H), 10.67 (br s, 1H); ^{13}C NMR δ 15.2, 29.1, 40.0, 47.8, 62.9, 100.9, 107.1, 108.45, 108.97, 119.2, 130.8, 159.4, 174.8; ESI-MS obsd 299.1732, calcd 299.1730 [(M + Na)$^+$, M = $C_{16}H_{24}N_2O_2$].

*2,3-Dihydro-1-[1,1-diethoxy(^{13}C)methyl]-3,3-dimethyldipyrrin (**1Et-^{13}C^{ac}**).* The above procedure with **2Et-^{13}C^1** (900 mg, 2.75 mmol) afforded the title compound as a dark brown oil (305 mg, 40%): ^{1}H NMR δ 1.21 (s, 6H), 1.26 (t, J = 7.1 Hz, 6H), 2.64 (s, 2H), 3.55−3.64 (m, 2H), 3.72−3.80 (m, 2H), 5.15 (d, J = 161 Hz, 1H), 5.87 (s, 1H), 6.14−6.17 (m, 2H), 6.83−6.84 (m, 1H), 10.67 (br s, 1H); ^{13}C NMR δ 15.2, 29.1, 40.0, 62.9, 100.9 (^{13}C), 107.1, 108.45, 108.97, 119.2, 130.8; ESI-MS obsd 278.1942, calcd 278.1194 [(M + H)$^+$, M = $C_{15}{}^{13}CH_{24}N_2O_2$].

Bacteriochlorins H_2BC. Note: employing anhydrous CH_3CN instead of HPLC-grade CH_3CN as solvent resulted in higher yields (9−16% versus 7−8%).

*8,8,18,18-Tetramethylbacteriochlorin (**H_2BC-NA**).* Following a standard procedure,[36] a solution of **1-NA** (487 mg, 1.96 mmol, 5.0 mM) in HPLC-grade CH_3CN (390 mL) was treated dropwise with neat $BF_3{\cdot}OEt_2$ (2.49 mL, 19.8 mmol, 50 mM) at room temperature. The reaction was allowed to proceed at room temperature for 16 h. TEA (3 mL) was added to the reaction mixture. The reaction mixture was then concentrated. Chromatography of the residue (silica, hexanes/CH_2Cl_2 (2/1)) afforded a green solid (28.4 mg, 8%): ^{1}H NMR δ −2.38 (br s, 2H), 1.97 (s, 12H), 4.47 (s, 4H), 8.72−8.74 (m, 2H), 8.73 (s, 2H), 8.76 (dd, J = 4.0 Hz, J = 1.8 Hz, 2H), 8.83 (s, 2H); ^{13}C NMR δ 31.1, 46.0, 51.4, 96.5, 98.7, 121.73, 121.84, 135.3, 136.2, 157.6; ESI-MS obsd 371.2223, calcd 371.2230 [(M + H)$^+$, M = $C_{24}H_{26}N_4$]; λ_{abs} (toluene) 340, 365, 489, 713 nm.

*8,8,18,18-Tetramethyl(21,23-$^{15}N_2$)bacteriochlorin (**H_2BC-^{15}N^{21,23}**).* The above procedure with **1-^{15}N^{11}** (934 mg, 3.75 mmol) afforded the title compound as a green solid (46.7 mg, 7%): ^{1}H NMR δ −2.39 (dt, J = 99 Hz, J = 2.0 Hz, 2H), 1.97 (s, 12H), 4.47 (s, 4H), 8.72−8.74 (m, 2H), 8.73 (d, J = 4.0 Hz, 2H), 8.76−8.78 (m, 2H), 8.84 (d, J = 4.8 Hz, 2H); ^{13}C NMR δ 31.1, 46.0, 51.4, 96.5, 98.6, 121.73 (d, J = 3.1 Hz), 121.84 (d, J = 3.8 Hz); ^{15}N NMR δ −249.3; ESI-MS obsd 373.2179, calcd 373.2171 [(M + H)$^+$, M = $C_{24}H_{26}N_2{}^{15}N_2$]; λ_{abs} (toluene) 340, 365, 489, 713 nm.

*8,8,18,18-Tetramethyl(22,24-$^{15}N_2$)bacteriochlorin (**H_2BC-^{15}N^{22,24}**).* The above procedure with **1-^{15}N^{10}** (487 mg, 1.96 mmol) afforded the title compound as a green solid (28.4 mg, 8%): ^{1}H NMR δ −2.39 (br s, 2H), 1.97 (s, 12H), 4.47 (s, 4H), 8.72−8.74 (m, 4H), 8.76 (dd, J = 4.4 Hz, J = 2.0 Hz, 2H) 8.83 (d, J = 4.8 Hz, 2H); ^{13}C NMR δ 31.1, 51.4, 96.5 (d, J = 3.8 Hz), 98.6 (d, J = 4.6 Hz), 121.72, 121.83; ^{15}N NMR δ −82.0; ESI-MS obsd 372.2093, calcd 372.2093 (M$^+$, M = $C_{24}H_{26}N_2{}^{15}N_2$); λ_{abs} (toluene) 340, 365, 489, 713 nm.

*8,8,18,18-Tetramethyl(1,11-$^{13}C_2$)bacteriochlorin (**H_2BC-^{13}C^{1,11}**).* The above procedure with **1-^{13}C^6** (460 mg, 1.85 mmol) in anhydrous CH_3CN afforded the title compound as a green solid (32.2 mg, 9%): ^{1}H NMR δ −2.38 (br s, 2H), 1.97 (s, 12H), 4.47 (s, 4H), 8.71−8.78 (m, 4H), 8.73 (d, J = 2.2 Hz, 2H), 8.84 (s, 2H); ^{13}C NMR δ 31.1, 46.0 (d, J = 3.8 Hz), 51.4, 96.5 (d, J = 70.2 Hz), 98.6, 121.72, 121.82 (d, J = 58.0 Hz), 135.3, 136.2 (^{13}C); ESI-MS obsd 373.2280, calcd 373.2297 [(M + H)$^+$, M = $C_{22}{}^{13}C_2H_{26}N_4$]; λ_{abs} (toluene) 340, 365, 489, 713 nm.

*8,8,18,18-Tetramethyl(4,14-$^{13}C_2$)bacteriochlorin (**H_2BC-^{13}C^{4,14}**).* The above procedure with **1-^{13}C^9** (615 mg, 2.47 mmol) in anhydrous CH_3CN afforded the title compound as a green solid (57.5 mg, 13%): ^{1}H NMR δ −2.38 (br s, 2H), 1.98 (s, 12H), 4.48 (s, 4H), 8.72−8.79 (m, 4H), 8.74 (s, 2H), 8.83 (d, J = 2.2 Hz, 2H); ^{13}C NMR δ 31.1, 46.0, 51.4 (d, J = 3.8 Hz), 96.5, 98.6 (d, J = 70.2 Hz), 121.71 (d, J = 58.0 Hz), 121.83, 135.3 (^{13}C), 136.2; ESI-MS obsd 372.2227, calcd 372.2219 (M$^+$, M = $C_{22}{}^{13}C_2H_{26}N_4$); λ_{abs} (toluene) 340, 365, 489, 713 nm.

*8,8,18,18-Tetramethyl(6,16-$^{13}C_2$)bacteriochlorin (**H_2BC-^{13}C^{6,16}**).* The above procedure with **1-^{13}C^1** (720 mg, 2.89 mmol) in anhydrous CH_3CN afforded the title compound as a green solid (74.9 mg, 14%): ^{1}H NMR δ −2.38 (br s, 2H), 1.98 (s, 12H), 4.48 (d, J = 5.1 Hz, 4H), 8.72−8.74 (m, 2H), 8.73 (s, 2H), 8.77 (dd, J = 4.0 Hz, J = 1.8 Hz, 2H), 8.84 (s, 2H); ^{13}C NMR δ 31.1, 51.4 (d, J = 38.2 Hz), 96.5 (d, J = 8.4 Hz), 98.6 (d, J = 74.0 Hz), 121.74 (d, J = 6.1 Hz), 121.84, 157.6 (^{13}C); ESI-MS obsd 373.2291, calcd 373.2297 [(M + H)$^+$, M = $C_{22}{}^{13}C_2H_{26}N_4$]; λ_{abs} (toluene) 340, 365, 489, 713 nm.

*8,8,18,18-Tetramethyl(9,19-$^{13}C_2$)bacteriochlorin (**H_2BC-^{13}C^{9,19}**).* The above procedure with **1-^{13}C^4** (1.16 g, 4.66 mmol) in anhydrous CH_3CN afforded the title compound as a green solid (76.3 mg, 9%): ^{1}H NMR δ −2.38 (br s, 2H), 1.97 (d, J = 3.7 Hz, 12H), 4.47 (s, 4H), 8.72−8.74 (m, 2H), 8.73 (s, 2H), 8.77 (dd, J = 4.4 Hz, J = 1.8 Hz, 2H), 8.84 (s, 2H); ^{13}C NMR δ 31.1, 51.4 (d, J = 5.3 Hz), 96.5 (d, J = 74.5 Hz), 98.7 (d, J = 8.4 Hz), 121.73, 121.84 (d, J = 6.1 Hz), 135.3, 169.6 (^{13}C); ESI-MS obsd 373.2294, calcd 373.2297 [(M + H)$^+$, M = $C_{22}{}^{13}C_2H_{26}N_4$]; λ_{abs} (toluene) 340, 365, 489, 713 nm.

*8,8,18,18-Tetramethyl(10,20-$^{13}C_2$)bacteriochlorin (**H_2BC-^{13}C^{10,20}**).* The above procedure with **1-^{13}C^5** (463 mg, 1.86 mmol) in anhydrous CH_3CN afforded the title compound as a green solid (54.8 mg, 16%): ^{1}H NMR δ −2.38 (br s, 2H), 1.97 (s, 12H), 4.47 (s, 4H), 8.73 (dd, J = 4.4 Hz, J = 1.8 Hz, 2H), 8.73 (d, J = 154 Hz, 2H), 8.75−8.78 (m, 2H), 8.83 (s, 2H); ^{13}C NMR δ 31.1, 54.4, 96.5 (^{13}C), 98.7, 121.73 (d, J = 4.6 Hz), 121.84 (d, J = 5.3 Hz); ESI-MS obsd 373.2297, calcd 373.2297 [(M + H)$^+$, M = $C_{22}{}^{13}C_2H_{26}N_4$]; λ_{abs} (toluene) 340, 365, 489, 713 nm.

dx.doi.org/10.1021/jo402488n | J. Org. Chem. 2014, 79, 1001−1016

*8,8,18,18-Tetramethylbacteriochlorin (**H$_2$BC-NA**) and 5-Ethoxy-8,8,18,18-tetramethylbacteriochlorin (**EtOBC-NA**) from **1Et-NA**.* The above procedure was carried out with **1Et-NA** (256 mg, 928 μmol, 5.0 mM) in anhydrous CH_3CN. Chromatography (silica, hexanes/CH_2Cl_2 (1/1)) afforded two green bands, which in order of elution consisted of **H$_2$BC-NA** (9.2 mg, 5%) and **EtOBC-NA** (3.8 mg, 2%). The characterization data for **H$_2$BC-NA** were consistent with those described above. Data for **EtOBC-NA**: ^{1}H NMR δ −2.27 (s, 1H), −2.14 (s, 1H), 1.84 (t, J = 7.0 Hz, 3H), 1.95 (s, 6H), 1.96 (s, 6H), 4.41 (s, 2H), 4.42 (s, 2H), 4.64 (q, J = 7.0 Hz, 2H), 8.66−8.69 (m, 3H), 8.66 (s, 1H), 8.70 (s, 1H), 8.74 (dd, J = 4.6 Hz, J = 2.0 Hz, 1H), 8.92 (dd, J = 4.4 Hz, J = 1.8 Hz, 1H); ESI-MS obsd 415.2494, calcd 415.2492 [(M + H)$^+$, M = $C_{26}H_{30}N_4O$]; λ_{abs} (CH_2Cl_2) 344, 354, 366, 500, 710 nm.

*8,8,18,18-Tetramethyl(5,15-$^{13}C_2$)bacteriochlorin (**H$_2$BC-^{13}C^{5,15}**).* The above procedure with **1Et-^{13}C^{ac}** (305 mg, 933 μmol) afforded the title compound as a green solid (5.8 mg, 3%): ^{1}H NMR δ −2.39 (br s, 2H), 1.97 (s, 12H), 4.47 (s, 4H), 8.72−8.84 (m, 2H), 8.73 (s, 2H), 8.77 (dd, J = 4.4 Hz, J = 2.0 Hz, 2H), 8.83 (d, J = 155 Hz, 2H); ^{13}C NMR δ 31.1, 51.4 (d, J = 6.9 Hz), 96.5, 98.7 (^{13}C), 121.73 (d, J = 5.3 Hz), 121.84 (d, J = 4.6 Hz); ESI-MS obsd 373.2292, calcd 373.2297 [(M + H)$^+$, M = $C_{22}{}^{13}C_2H_{26}N_4$]; λ_{abs} (toluene) 340, 365, 489, 713 nm.

Zinc Bacteriochlorins {ZnBC}. *Zn(II)−8,8,18,18-Tetramethyl-(21,23-$^{15}N_2$)bacteriochlorin (**ZnBC-^{15}N^{21,23}**).* Following a standard procedure,[35] a solution of **H$_2$BC-^{15}N^{21,23}** (5.8 mg, 16 μmol, 4 mM) in freshly distilled THF (4 mL) was treated with NaH (54 mg, 2.3 mmol, 150 equiv, 95%) and $Zn(OTf)_2$ (176 mg, 0.484 mmol, 30 equiv). The reaction mixture was heated at 60 °C for 16 h. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and filtered. The filtrate was concentrated. The crude solid was treated with hexanes, sonicated in a benchtop sonication bath, and centrifuged, and the supernatant was discarded. A single repetition of the hexanes treatment afforded a dark red solid (2.4 mg, 35%): ^{1}H NMR (THF-d_8) δ 1.97 (s, 12H), 4.46 (s, 4H), 8.60−8.62 (m, 4H), 8.64−8.66 (m, 4H); ESI-MS obsd 434.1212, calcd 434.1228 ($C_{24}H_{24}N_2{}^{15}N_2Zn$); λ_{abs} (toluene) 336, 375, 514, 723 nm. (A peak at ∼433 m/z was found in the ESI-mass spectrum yet did not match the exact mass of a bacteriochlorin bearing one ^{15}N atom. Given that the ESI-mass spectrum of the corresponding **CuBC-^{15}N^{21,23}** does not show such a peak, we consider no isotopic loss in **ZnBC-^{15}N^{21,23}**; see the Supporting Information.)

*Zn(II)−8,8,18,18-Tetramethyl(22,24-$^{15}N_2$)bacteriochlorin (**ZnBC-^{15}N^{22,24}**).* The above procedure with **H$_2$BC-^{15}N^{22,24}** (5.6 mg, 15 μmol) afforded the title compound as a dark red solid (4.6 mg, 71%): ^{1}H NMR (THF-d_8) δ 1.98 (s, 12H), 4.46 (s, 4H), 8.60−8.62 (m, 4H), 8.64−8.66 (m, 4H); ESI-MS obsd 434.1235, calcd 434.1228 ($C_{24}H_{24}N_2{}^{15}N_2Zn$); λ_{abs} (toluene) 336, 375, 514, 723 nm.

*Zn(II)−8,8,18,18-Tetramethyl(1,11-$^{13}C_2$)bacteriochlorin (**ZnBC-^{13}C^{1,11}**).* The above procedure with **H$_2$BC-^{13}C^{1,11}** (3.7 mg, 10 μmol) afforded the title compound as a dark red solid (3.2 mg, 73%): ^{1}H NMR (THF-d_8) δ 1.97 (s, 12H), 4.46 (s, 4H), 8.59−8.66 (m, 8H); ESI-MS obsd 434.1362, calcd 434.1354 ($C_{22}{}^{13}C_2H_{24}N_4Zn$); λ_{abs} (toluene) 336, 375, 514, 723 nm.

*Zn(II)−8,8,18,18-Tetramethyl(4,14-$^{13}C_2$)bacteriochlorin (**ZnBC-^{13}C^{4,14}**).* The above procedure with **H$_2$BC-^{13}C^{4,14}** (3.7 mg, 10 μmol) afforded the title compound as a dark red solid (2.2 mg, 50%): ^{1}H NMR (THF-d_8) δ 1.97 (s, 12H), 4.46 (br s, 4H), 8.59−8.67 (m, 6H), 8.60 (s, 2H); ESI-MS obsd 434.1359, calcd 434.1354 ($C_{22}{}^{13}C_2H_{24}N_4Zn$); λ_{abs} (toluene) 336, 375, 514, 723 nm.

*Zn(II)−8,8,18,18-Tetramethyl(5,15-$^{13}C_2$)bacteriochlorin (**ZnBC-^{13}C^{5,15}**).* The above procedure with **H$_2$BC-^{13}C^{5,15}** (2.9 mg, 7.8 μmol) afforded the title compound as a dark red solid (2.8 mg, 83%): ^{1}H NMR (THF-d_8) δ 1.98 (s, 12H), 4.46 (s, 4H), 8.60−8.62 (m, 4H), 8.64 (d, J = 152.5 Hz 2H), 8.65 (d, J = 4.1 Hz, 2H); ESI-MS obsd 434.1355, calcd 434.1354 ($C_{22}{}^{13}C_2H_{24}N_4Zn$); λ_{abs} (toluene) 336, 375, 514, 723 nm.

*Zn(II)−8,8,18,18-Tetramethyl(6,16-$^{13}C_2$)bacteriochlorin (**ZnBC-^{13}C^{6,16}**).* The above procedure with **H$_2$BC-^{13}C^{4,14}** (5.8 mg, 16 μmol) afforded the title compound as a dark red solid (4.8 mg, 69%): ^{1}H NMR (THF-d_8) δ 1.97 (s, 12H), 4.46 (br s, 4H), 8.60−8.62 (m, 4H), 8.64−8.66 (m, 4H); ESI-MS obsd 434.1355, calcd 434.1354 ($C_{22}{}^{13}C_2H_{24}N_4Zn$); λ_{abs} (toluene) 336, 375, 514, 723 nm.

*Zn(II)−8,8,18,18-Tetramethyl(9,19-$^{13}C_2$)bacteriochlorin (**ZnBC-^{13}C^{9,19}**).* The above procedure with **H$_2$BC-^{13}C^{9,19}** (5.8 mg, 16 μmol) afforded the title compound as a dark red solid (2.8 mg, 40%): ^{1}H NMR (THF-d_8) δ 1.97−1.98 (m, 12H), 4.46 (br s, 4H), 8.60−8.62 (m, 4H), 8.64−8.66 (m, 4H); ESI-MS obsd 434.1362, calcd 434.1354 ($C_{22}{}^{13}C_2H_{24}N_4Zn$); λ_{abs} (toluene) 336, 375, 514, 723 nm.

*Zn(II)−8,8,18,18-Tetramethyl(10,20-$^{13}C_2$)bacteriochlorin (**ZnBC-^{13}C^{10,20}**).* The above procedure with **H$_2$BC-^{13}C^{10,20}** (5.8 mg, 16 μmol) afforded the title compound as a dark red solid (4.1 mg, 59%): ^{1}H NMR (THF-d_8) δ 1.97 (s, 12H), 4.46 (s, 4H), 8.60 (d, $^1J_{CH}$ = 151.4 Hz, 2H), 8.61 (d, J = 4.4 Hz, 2H), 8.64 (s, 2H), 8.65 (d, J = 4.4 Hz, 2H); ESI-MS obsd 434.1345, calcd 434.1354 ($C_{22}{}^{13}C_2H_{24}N_4Zn$); λ_{abs} (toluene) 336, 375, 514, 723 nm.

Copper Bacteriochlorins {CuBC}. The reaction is sensitive to moisture. In the case that the reaction was not complete in 16 h, a supplement of NaH (150 equiv) or LDA (10 equiv) was added and the reaction mixture was heated at 60 °C for a further 8−16 h. Use of $Cu(OAc)_2$ dried in an oven for 36 h at 100 °C before use significantly shortened the reaction time (typically <16 h). When LDA was used, the crude mixture was chromatographed (silica, hexanes/CH_2Cl_2 (1/2)) to afford the **CuBC**.

*Cu(II)−8,8,18,18-Tetramethyl(21,23-$^{15}N_2$)bacteriochlorin (**CuBC-^{15}N^{21,23}**).* Following a standard procedure,[35] a solution of **H$_2$BC-^{15}N^{21,23}** (6.1 mg, 16 μmol, 4 mM) in freshly distilled THF (4 mL) was treated with NaH (54 mg, 2.3 mmol, 150 equiv, 95%) and $Cu(OAc)_2$ (90 mg, 0.49 mmol, 30 equiv). The reaction mixture was heated at 60 °C for 16 h. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and filtered. The filtrate was concentrated. The crude solid was treated with hexanes, sonicated in a benchtop sonication bath, and centrifuged, and the supernatant was discarded. A single repetition of the hexanes treatment afforded a green solid (1.9 mg, 27%): ESI-MS obsd 433.1235, calcd 433.1232 ($C_{24}H_{24}N_2{}^{15}N_2Cu$); λ_{abs} (toluene) 332, 378, 507, 728 nm.

*Cu(II)−8,8,18,18-Tetramethyl(22,24-$^{15}N_2$)bacteriochlorin (**CuBC-^{15}N^{22,24}**).* The above procedure with **H$_2$BC-^{15}N^{22,24}** (5.8 mg, 16 μmol) afforded the title compound as a green solid (3.4 mg, 49%): ESI-MS obsd 433.1234, calcd 433.1232 ($C_{24}H_{24}N_2{}^{15}N_2Cu$); λ_{abs} (toluene) 332, 378, 507, 728 nm.

*Cu(II)−8,8,18,18-Tetramethyl(1,11-$^{13}C_2$)bacteriochlorin (**CuBC-^{13}C^{4,14}**).* The above procedure with **H$_2$BC-^{13}C^{4,14}** (5.8 mg, 16 μmol) afforded the title compound as a green solid (1.9 mg, 28%): ESI-MS obsd 433.1364, calcd 433.1359 ($C_{22}{}^{13}C_2H_{24}N_4Cu$); λ_{abs} (toluene) 332, 378, 507, 728 nm.

*Cu(II)−8,8,18,18-Tetramethyl(4,14-$^{13}C_2$)bacteriochlorin (**CuBC-^{13}C^{4,14}**).* The above procedure with **H$_2$BC-^{13}C^{6,16}** (5.8 mg, 16 μmol) afforded the title compound as a green solid (2.0 mg, 30%): ESI-MS obsd 433.1358, calcd 433.1359 ($C_{22}{}^{13}C_2H_{24}N_4Cu$); λ_{abs} (toluene) 332, 378, 507, 728 nm.

*Cu(II)−8,8,18,18-Tetramethyl(5,15-$^{13}C_2$)bacteriochlorin (**CuBC-^{13}C^{5,15}**).* The above procedure with **H$_2$BC-^{13}C^{5,15}** (5.8 mg, 16 μmol) afforded the title compound as a green solid (2.8 mg, 40%): ESI-MS obsd 433.1352, calcd 433.1359 ($C_{22}{}^{13}C_2H_{24}N_4Cu$); λ_{abs} (toluene) 332, 378, 507, 728 nm.

*Cu(II)−8,8,18,18-Tetramethyl(6,16-$^{13}C_2$)bacteriochlorin (**CuBC-^{13}C^{6,16}**).* The above procedure with **H$_2$BC-^{13}C^{6,16}** (5.8 mg, 16 μmol) afforded the title compound as a green solid (5.3 mg, 77%): ESI-MS obsd 433.1362, calcd 433.1359 ($C_{22}{}^{13}C_2H_{24}N_4Cu$); λ_{abs} (toluene) 332, 378, 507, 728 nm.

*Cu(II)−8,8,18,18-Tetramethyl(9,19-$^{13}C_2$)bacteriochlorin (**CuBC-^{13}C^{9,19}**).* The above procedure with **H$_2$BC-^{13}C^{9,19}** (5.8 mg, 16 μmol) afforded the title compound as a green solid (4.7 mg, 69%): ESI-MS obsd 433.1364, calcd 433.1359 ($C_{22}{}^{13}C_2H_{24}N_4Cu$); λ_{abs} (toluene) 332, 378, 507, 728 nm.

*Cu(II)−8,8,18,18-Tetramethyl(10,20-$^{13}C_2$)bacteriochlorin (**CuBC-^{13}C^{10,20}**).* The above procedure with **H$_2$BC-^{13}C^{10,20}** (5.8 mg, 16 μmol) afforded the title compound as a green solid (5.3 mg, 77%):

dx.doi.org/10.1021/jo402488n | J. Org. Chem. 2014, 79, 1001−1016

ESI-MS obsd 433.1343, calcd 433.1359 ($C_{22}{}^{13}C_2H_{24}N_4Cu$); λ_{abs} (toluene) 332, 378, 507, 728 nm.

■ ASSOCIATED CONTENT

Supporting Information

Text, figures, tables, and a CIF file giving X-ray data for **10-NA** (CCDC 978333), comparison of syntheses of nitrohexanone–pyrrole **2**, buffer calculations for use of $TiCl_3$ in dihydropyrrin–acetal formation, NMR chemical shift assignments, method for determination of isotopic enrichment, ^1H, ^{13}C, and ^{15}N NMR spectra for all new compounds, and ESI mass spectra for {**H_2BC**}, {**ZnBC**}, and {**CuBC**}. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by grants from the Division of Chemical Sciences, Geosciences, and Biosciences, Office of Basic Energy Sciences of the U.S. Department of Energy, to D.F.B. (DE-FG02-05ER15660) and J.S.L. (DE-FG02-96ER14632). Mass spectra were obtained at the Mass Spectrometry Laboratory for Biotechnology at North Carolina State University. Partial funding for the facility was obtained from the North Carolina Biotechnology Center and the National Science Foundation.

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