Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 63 (2007) 37–55
Tetrahedron

Synthesis of hydrodipyrrins tailored for reactivity at the 1- and 9-positions

Han-Je Kim, Dilek Kiper Dogutan, Marcin Ptaszek and Jonathan S. Lindsey*

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

Received 9 August 2006; revised 5 October 2006; accepted 9 October 2006
Available online 1 November 2006

Abstract—A collection of 33 hydrodipyrrins (9 targets, 21 intermediates, and 3 byproducts) has been prepared. The hydrodipyrrins (dihydrodipyrrins, tetrahydrodipyrrins, and hexahydrodipyrrins) contain a pyrrole ring and a geminal-dimethyl substituted 1-pyrroline (or pyrrolidine) ring. The α-substituents on the pyrrole ring (H, Br, CHO) and pyrroline ring (H, CH_3, $CH(OR)_2$, OMe, SMe) provide different reactivity combinations (Nu^-, E^+) and 0, 1, or 2 carbon atoms (which can give rise to the bridging *meso*-carbons in hydroporphyrins). Straightforward access to various hydrodipyrrins should facilitate development of syntheses of diverse hydroporphyrins.

---

1. Introduction

Hydroporphyrins perform a wide variety of essential functions in living systems. Hydroporphyrins differ from porphyrins in having fewer π bonds along the perimeter of the macrocycle. Representative hydroporphyrins are shown in Chart 1. Chlorophylls *a* and *b* (chlorins) and bacteriochlorophylls *a*, *b*, and *g* (bacteriochlorins) serve as the principal light-absorbing pigments in plant and bacterial photosynthetic systems, respectively.[1] Bonellin[2] and tolyporphins[3] are examples of non-photosynthetic chlorin and bacteriochlorin macrocycles, respectively. Siroheme and heme d_1 (isobacteriochlorins) play an important role in the sulfur and nitrogen metabolism of numerous microorganisms.[4] A wide variety of other naturally occurring hydroporphyrins (e.g., vitamin B_{12}[5] and F_{430}[6]) are known.

Fundamental chemical studies, biological investigations, and materials chemistry applications require efficient routes for preparing the core hydroporphyrins. The simplest approach to chlorins, bacteriochlorins, and isobacteriochlorins entails hydrogenation of the porphyrin.[7] The simplicity of this approach is often offset by two problems: (1) reduction in any of the four pyrrolic rings yields regioisomers if a distinct pattern of peripheral substituents is present, and (2) the hydroporphyrin is susceptible to adventitious dehydrogenation. By contrast, the most complex approach entails the total synthesis of naturally occurring hydroporphyrins.[8] Semisynthetic approaches also have been employed to manipulate chlorins without incurring the enormous effort required for the total synthesis.[9]

A middle approach, which we have pursued, is to develop de novo syntheses of model hydroporphyrins that retain most of the essential physicochemical properties of the natural compounds yet have non-natural structural attributes that facilitate synthesis and handling.[10–15] A key structural feature that we have employed is the use of a geminal-dimethyl group in each reduced ring. The geminal-dimethyl group locks in the reduction level of the resulting hydroporphyrin, thereby precluding adventitious oxidative reversion to the porphyrin. Many naturally occurring hydroporphyrins have a geminal dialkyl group in each reduced pyrroline ring (e.g., bonellin, tolyporphin, siroheme, heme d_1, F_{430}, and vitamin B_{12}). Although chlorophylls and bacteriochlorophylls lack the geminal dialkyl motif, synthetic analogues that contain a geminal dialkyl group in the pyrroline ring exhibit characteristic chlorin or bacteriochlorin features and are quite stable compounds.[10–15]

The de novo syntheses that we developed for chlorins, which drew heavily on methods established in the total synthesis of bonellin,[16,17] are shown in Scheme 1. Each de novo synthesis involves the convergent joining of an Eastern half and a Western half. Two Western halves, a dihydrodipyrrin (**1**)[10] and a tetrahydrodipyrrin (**2**),[12,18] were each synthesized in four to five steps from pyrrole-2-carboxaldehyde. Acid-catalyzed condensation of a bromo-dipyrromethane-carbinol (Eastern half, **3a**) and **1** or **2** followed by oxidative cyclization afforded the *meso*-disubstituted zinc chlorin **4a**. The cyclization yield reached up to 45% depending on the presence of substituents in the components and the choice of Western half.[10–13] A related synthesis uses

---

Keywords: Hydrodipyrrin; 1-Pyrroline; Pyrrole; Hydroporphyrin.
* Corresponding author. Tel.: +1 9195156406; fax: +1 9195132830; e-mail: jlindsey@ncsu.edu

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.10.027

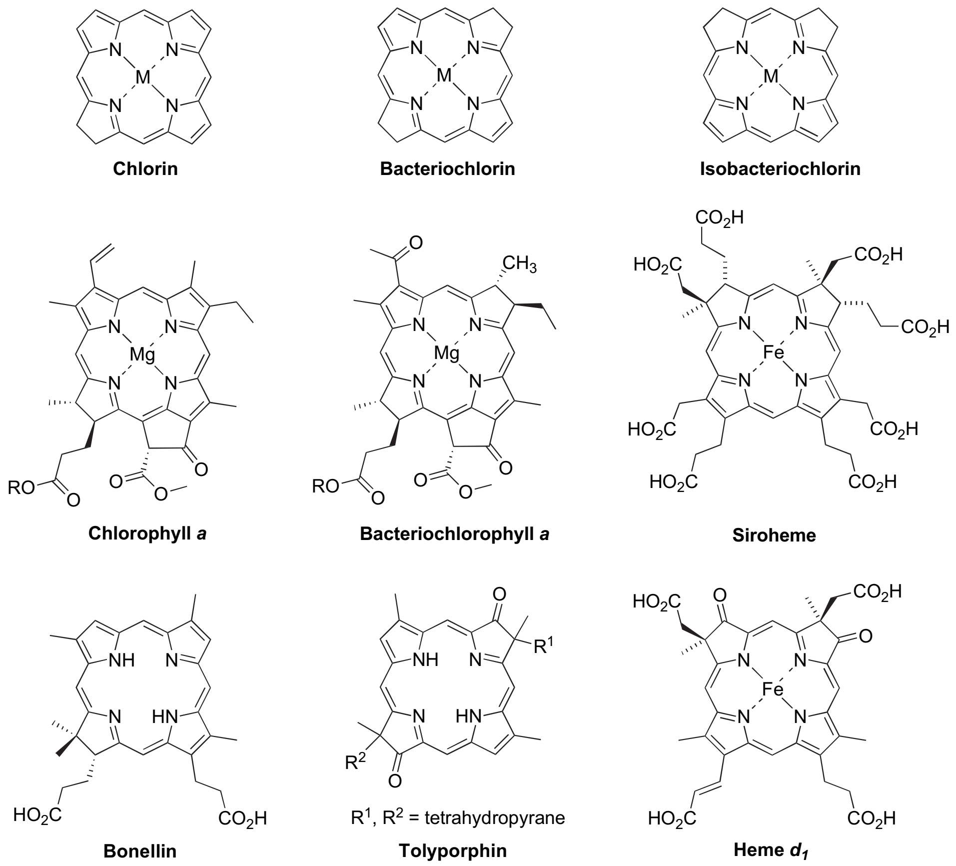
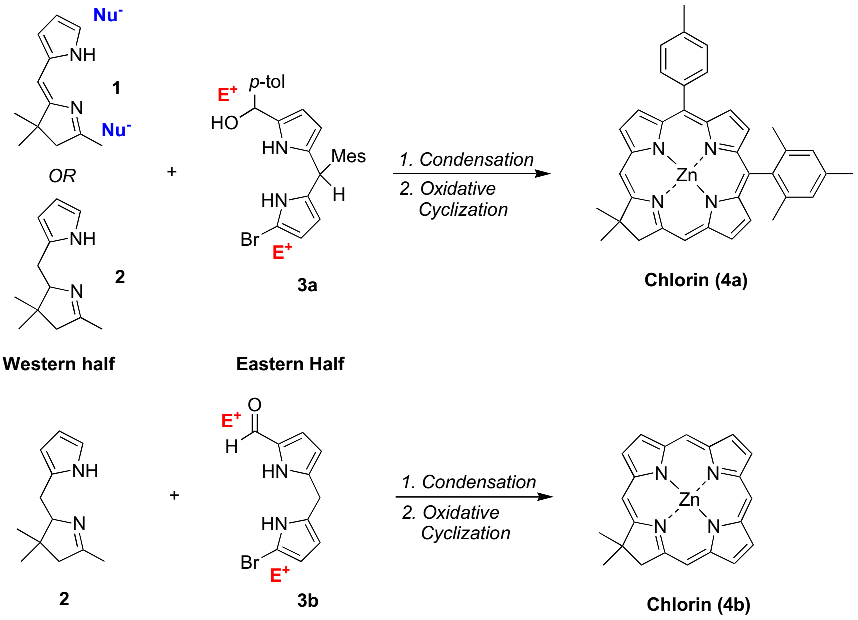


Chart 1.

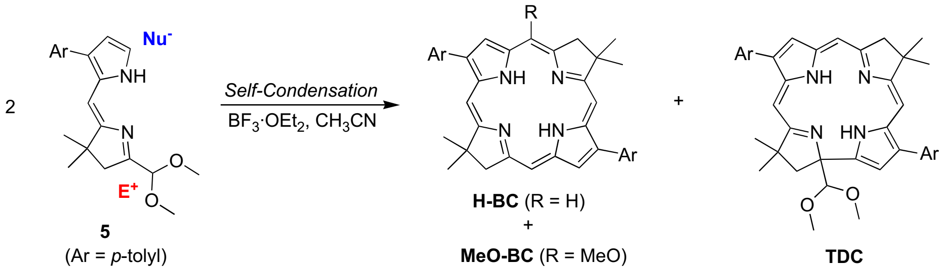
a formyl-containing Eastern half (**3b**) to give the fully unsubstituted zinc chlorin **4b**.[14]

The de novo synthesis of bacteriochlorins is shown in Scheme 2. A dihydrodipyrrin bearing an acetal moiety (**5**) undergoes self-condensation under acidic conditions at room temperature. Two bacteriochlorins (**H-BC**, **MeO-BC**) were obtained as well as the ring-contracted analogue, a tetradehydrocorrin (**TDC**).[15]

The strategy underlying each such '2+2' route to hydroporphyrins depends on the nature of the substituents at the α-positions of the hydrodipyrrins. In the chlorin synthesis,[10–14] the pyrrole unit and the α-methyl pyrroline unit of



Scheme 1.



Scheme 2.

the hydrodipyrrin (Western half) both functioned as nucleophiles, the two complementary sites on the Eastern half (bromopyrrole, α-carbinol) functioned as electrophiles, and each half contributed one bridging *meso*-carbon atom (Scheme 1). In the bacteriochlorin synthesis,[15] the pyrrole unit and the α-acetal-pyrroline unit functioned as nucleophile and electrophile, respectively, and the acetal provided the bridging *meso*-carbon atom (Scheme 2). In general, the development of new 2+2 reactions for preparing hydroporphyrins relies on access to hydrodipyrrins with suitable reactivity at the α-position of the respective pyrrole or pyrroline unit.

A wide variety of dihydrodipyrrin species bearing diverse α-substituents have been developed for the syntheses of naturally occurring chlorins and isobacteriochlorins.[16,17,19–29] (By contrast, the tetrahydrodipyrrins prepared to date are fewer in number and typically contain the same α-substituents as those of **2**.[23,24,30]) The representative collection of dihydrodipyrrins (**A**–**F**) shown in Chart 2 illustrates the substituents at the pyrroline and pyrrole α-positions that have been employed to engender distinct nucleophilic or electrophilic reactivity features. The reactivity includes an electrophilic pyrrole (α-formyl: **A**,[27] **B**,[27] and **D**[20,21,23–26]), nucleophilic pyrrole (no α-substituent: **C**,[17] and **E**[27] and **F**[27] upon decarboxylation), nucleophilic pyrroline (α-methyl, which forms an enamine: **A**, **C**), and electrophilic pyrroline via leaving groups (α-formyl: **B**, **E**; α-(thio)alkoxide: **D**, **F**; or α-triflate: **F**) or via an α-unsubstituted pyrroline *N*-oxide[22] (not shown). The number of α-carbon atoms, which potentially confer bridging *meso*-carbon atoms upon hydroporphyrin formation, is two (**A**, **B**), one (**C**–**E**), or zero (**F**). Most of the dihydrodipyrrins bear substituents at one or both β-pyrrole positions as required for the synthesis of naturally occurring hydroporphyrins.

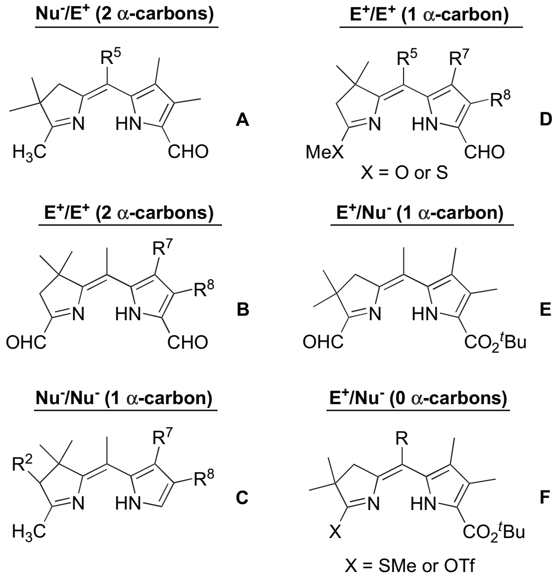


Chart 2.

Synthetic hydroporphyrins with few or no substituents could serve as valuable benchmarks for understanding fundamental properties and reactivity. However, the syntheses of such sparsely substituted hydroporphyrins have proved to be more difficult than those bearing a full complement of pyrrole substituents, owing to the broader range of possible side reactions of the unsubstituted hydrodipyrrin precursors.

In this regard, the simple appearance of unsubstituted hydrodipyrrins can be deceptive, because the two different heterocycles (pyrrole, 1-pyrroline) exhibit distinct reactivity features.[18] A number of these differences are quite obvious: the pyrrole in **1** or **2** is activated at three sites (7-, 8-, and 9-position) for electrophilic substitution whereas the imine is susceptible to reduction and addition; the pyrrole is a weak acid whereas the pyrroline is a weak base. The coordination ability of hydrodipyrrins can thwart a number of metal-mediated reactions. Perhaps less obviously, tetrahydrodipyrrins lacking β-pyrrole substituents (e.g., **2**) can undergo irreversible intramolecular cyclization in the presence of acid, forming a bicyclic, tropane-like structure.[12] Thus, the scope of suitable synthetic methods for preparing and manipulating synthetic hydrodipyrrins, particularly those lacking β-pyrrole substituents, is somewhat constrained.

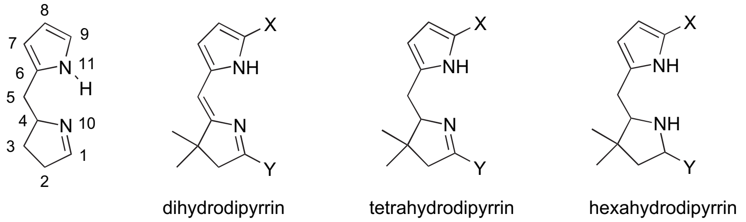
In this paper, we describe the synthesis of new hydrodipyrrins, chiefly tetrahydrodipyrrins, with a variety of groups at the pyrrole and pyrroline α-positions. The emphasis on tetrahydrodipyrrins stems from studies in chlorin chemistry[12] where unsubstituted tetrahydrodipyrrins (e.g., **2**) were found to have a substantially longer shelf-life than the corresponding dihydrodipyrrins (e.g., **1**). The hydrodipyrrins lack β-pyrrole and *meso*-substituents. The availability of this set of compounds should provide a valuable toolkit for investigating the syntheses of a variety of hydroporphyrins.

2. Results and discussion

2.1. Approach

The target hydrodipyrrins are illustrated in Table 1. The hydrodipyrrins in each class differ in the pattern of reactivity (Nu^-/E^+) and number of C_1 synthons (0–2) attached at the

Table 1. Target hydrodipyrrins



Entry	α-Carbons	Reactivity type (substituent)	
		Pyrroline (-Y)	Pyrrole (-X)
I	0	E$^+$ (H, OMe, SMe)	Nu$^-$ (H)
II	1	E$^+$ (CHO)	Nu$^-$ (H)
III	1	E$^+$ (CHO)	E$^+$ (Br)
IV	2	E$^+$ (CHO)	E$^+$ (CHO)
V	1	Nu$^-$ (CH$_3$)	E$^+$ (Br)
VI	2	Nu$^-$ (CH$_3$)	E$^+$ (CHO)

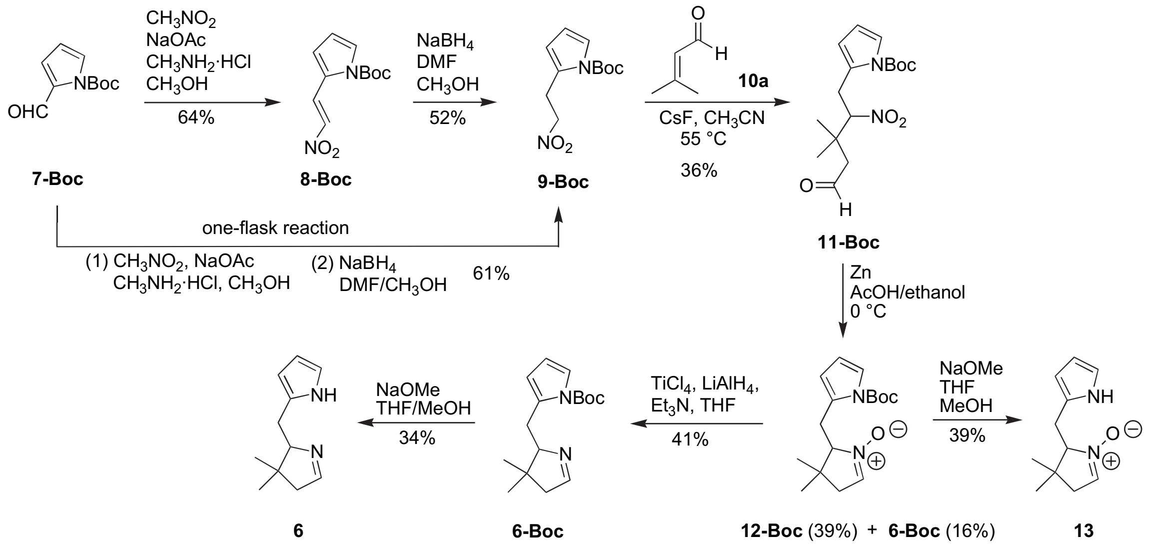
1- and 9-positions. While our chief focus centered on tetrahydrodipyrrins, we also examined dihydrodipyrrins and hexahydrodipyrrins to a limited extent. The following sections describe the routes that afforded the target compounds, protected analogues, and related derivatives.

2.2. Synthesis of hydrodipyrrins

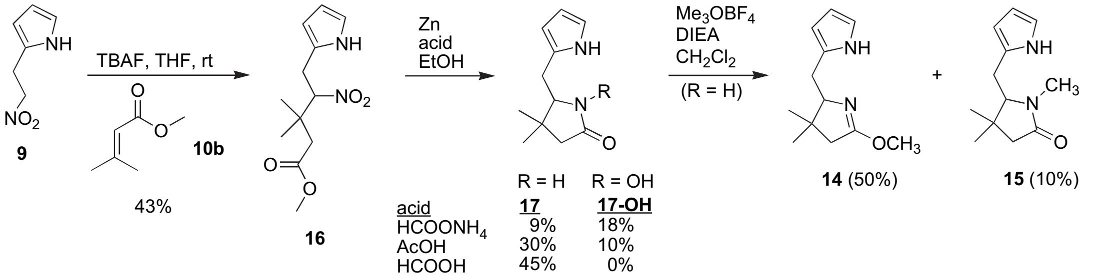
2.2.1. E$^+$/Nu$^-$ pyrroline–pyrrole units (0 α-carbons).

2.2.1.1. Imines. An initial target was an analogue of **2** lacking a methyl group at the α-position of the pyrroline ring (**6**). Analogues of such 'des-methyl' species bearing β-pyrrolic substituents were important precursors in Battersby's synthesis of isobacteriochlorins.[22] Thus, *N*-Boc-pyrrole-2-carboxaldehyde (**7-Boc**)[31] was converted via the intermediate nitrovinyl pyrrole **8-Boc** to the nitroethylpyrrole **9-Boc** in either a two-step or one-flask process (Scheme 3). The Michael addition of **9-Boc** with 3-methyl-2-butenal (**10a**) gave the nitropentanal-pyrrole **11-Boc** (36% yield), which upon cyclization in the presence of Zn and acetic acid afforded the expected *N*-oxide (**12-Boc**, 39%) and the deoxygenated *N*-Boc tetrahydrodipyrrin **6-Boc** (16%). Two routes were investigated to obtain **6** from the *N*-oxide **12-Boc**, which differ in the order of deoxygenation and cleavage of the Boc group. Removal of the Boc group upon treatment with NaOMe afforded the *N*-oxide **13**, which proved to be slightly unstable. On the other hand, deoxygenation of **12-Boc** with Ti(0) gave **6-Boc** (41% yield), which upon subsequent treatment with NaOMe gave the target compound **6** in 34% yield.

2.2.1.2. Imidates. The electrophilicity of the α-pyrroline position can be altered by the introduction of a leaving group. The synthesis of the corresponding tetrahydrodipyrrin-imidate (**14**) is shown in Scheme 4. The Michael addition of **9**[18] with methyl 3,3-dimethylacrylate (**10b**) was examined under several conditions. The desired methyl nitropentanoate **16** was obtained upon reaction at 65 °C via a solventless synthesis with DBU (20% yield), with DBU in acetonitrile (19% yield), or CsF in acetonitrile (11% yield). On the other hand, the use of TBAF in acetonitrile at room temperature gave **16** in 43% yield (see Section 4).



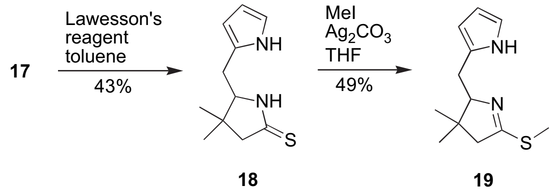
Scheme 3.



Scheme 4.

The reductive cyclization of nitroester **16** also was carried out under several conditions. Zn/HCO_2NH_4[18] or Zn/AcOH[12] afforded the mixture of lactam **17** (9% or 30% yield) or hydroxamic acid **17**-**OH** (18% or 10% yield), respectively. The cleanest reaction and the highest yield were obtained with Zn/HCO_2H[32] in EtOH at room temperature, affording **17** in 45% yield. The reaction of **17** with trimethyloxonium tetrafluoroborate in anhydrous CH_2Cl_2 containing *N*,*N*-diisopropylethylamine (DIEA) provided the *O*-methylated product **14** in 50% yield (together with the *N*-methyl lactam **15** in 10% yield).

2.2.1.3. Thioimidates. The greater reactivity of thioesters and thioimidates versus the oxygen analogues[23,33] toward nucleophilic substitution prompted the synthesis of tetrahydrodipyrrin-thioimidates. Thus, treatment of lactam **17** with Lawesson's reagent[34] in toluene afforded thiolactam **18** in 43% yield. The attempted *S*-alkylation of **18** using Meerwein's salt gave multiple products, whereas methyl iodide in the presence of silver(I) carbonate[24] afforded the expected *S*-methylsulfanyl product **19** in 49% yield (Scheme 5).



Scheme 5.

In summary, tetrahydrodipyrrins **6**, **14**, and **19** contain no α-carbons and meet the target criteria of E^+/Nu^- reactivity at the 1- and 9-positions.

2.2.2. E^+/Nu^- pyrroline–pyrrole units (1 α-carbon).

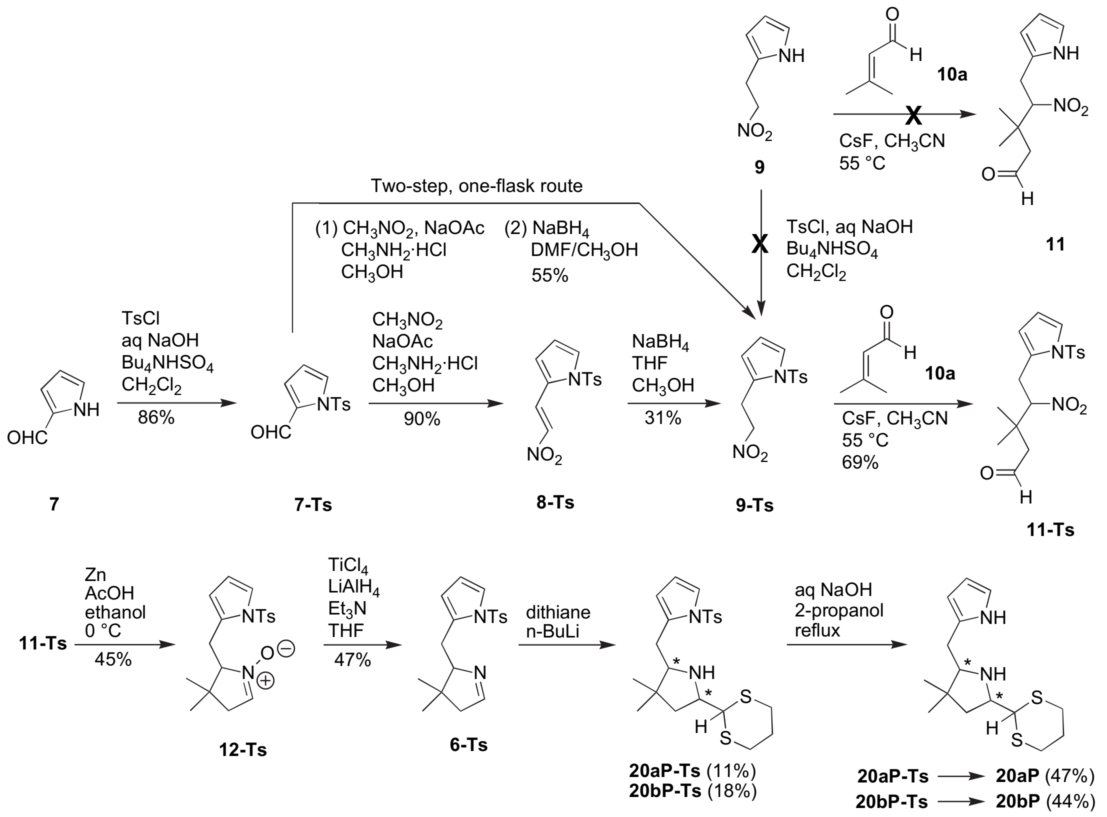
2.2.2.1. Hexahydrodipyrrin-dithiane. The synthesis of the dithiane analogue (**20P**) of hexahydropyrrin-aldehyde **20** was initially attempted via 2-(2-nitroethyl)pyrrole (**9**) in the same manner as for **2**. However, the Michael addition of **9** with the aldehyde **10a** gave multiple products. To suppress the reactivity of **9** we turned to the *p*-tosyl protecting group.[35–37] The direct *p*-tosylation of nitroethylpyrrole **9** to give **9**-**Ts** was unsuccessful, requiring introduction of the *p*-tosyl group at the outset of the synthesis (Scheme 6).

The reaction of pyrrole-2-carboxaldehyde (**7**) and *p*-tosyl chloride under phase-transfer conditions afforded the *N*-*p*-tosyl derivative **7**-**Ts** (a known compound[37] but with previously incomplete characterization data) in 86% yield. The subsequent nitro-aldol condensation and reduction were initially performed in two steps via the intermediate nitrovinylpyrrole **8**-**Ts** to give *N*-*p*-tosyl nitroethylpyrrole **9**-**Ts**. An alternative two-step, one-flask synthesis[13] proved to be simpler and afforded a higher yield of **9**-**Ts** (55% vs 28%). Michael addition of the latter with **10a** in the presence of CsF at 55 °C gave the nitropentanal-pyrrole **11**-**Ts** in 69% yield.

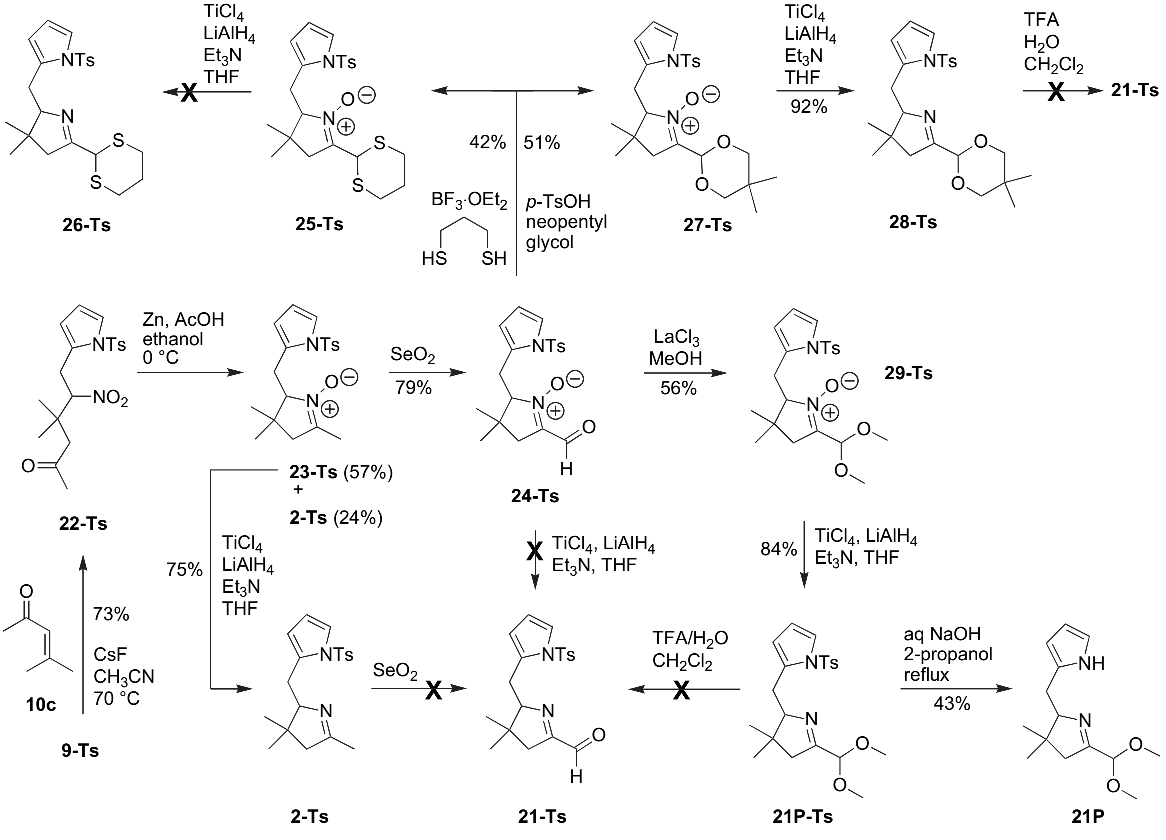
Reductive cyclization of **11**-**Ts** in the presence of Zn in acetic acid and ethanol at 0 °C afforded the *N*-oxide **12**-**Ts** in 45% yield. Deoxygenation of **12**-**Ts** gave the *N*-protected **6**-**Ts** in 47% yield. Dithiane addition[38] to the imine of **6**-**Ts** gave two separable diastereomers (**20aP**-**Ts**, **20bP**-**Ts**) in 29% overall yield. The *p*-tosyl group of each diastereomer was removed using aqueous NaOH and 2-propanol. The resulting **20aP** and **20bP** are protected derivatives of target hexahydrodipyrrin-aldehyde **20**. We note that **20** would contain an α-aminoaldehyde, a motif prone to tautomerization,[39] but could provide a valuable precursor to bacteriochlorins if conditions are identified where condensation is a competitive process.

2.2.2.2. Tetrahydrodipyrrin- and dihydrodipyrrin-acetal. We examined the direct oxidation of the α-methyl group in pyrroline **2** to afford aldehyde **21** using SeO_2,[27] but were unable to identify suitable conditions for this apparently simple transformation. Given that the *N*-oxide in a pyrroline ring accelerates oxidative conversion of the α-methyl group to the aldehyde,[40] we turned to the pyrroline *N*-oxide. Michael addition of **9**-**Ts** with mesityl oxide (**10c**) gave **22**-**Ts**, which upon reductive cyclization gave the tetrahydrodipyrrin *N*-oxide **23**-**Ts** accompanied by the fully deoxygenated **2**-**Ts** (Scheme 7). Treatment of **23**-**Ts** with freshly prepared Ti(0)[13] afforded **2**-**Ts** in 75% yield. Oxidation of *N*-oxide **23**-**Ts** with SeO_2 gave the corresponding aldehyde **24**-**Ts** in 79% yield. Attempted deoxygenation of both **2**-**Ts** and **24**-**Ts** failed to give **21**-**Ts**.

The failure of the direct deoxygenation of **24**-**Ts** prompted investigation of aldehyde protecting groups. Use of 1,3-propanedithiol[41] gave compound **25**-**Ts**, which was unstable (e.g., decomposed after 24 h in $CDCl_3$). Attempts to deoxygenate **25**-**Ts** were not successful, which can be attributed to its instability. Use of neopentyl glycol[42,43] gave *N*-oxide **27**-**Ts**, which upon deoxygenation gave acetal **28**-**Ts** in 92% yield. Although **28**-**Ts** was stable, the subsequent hydrolysis to give **21**-**Ts** also was unsuccessful. Finally, **24**-**Ts** was converted to the more labile dimethyl acetal



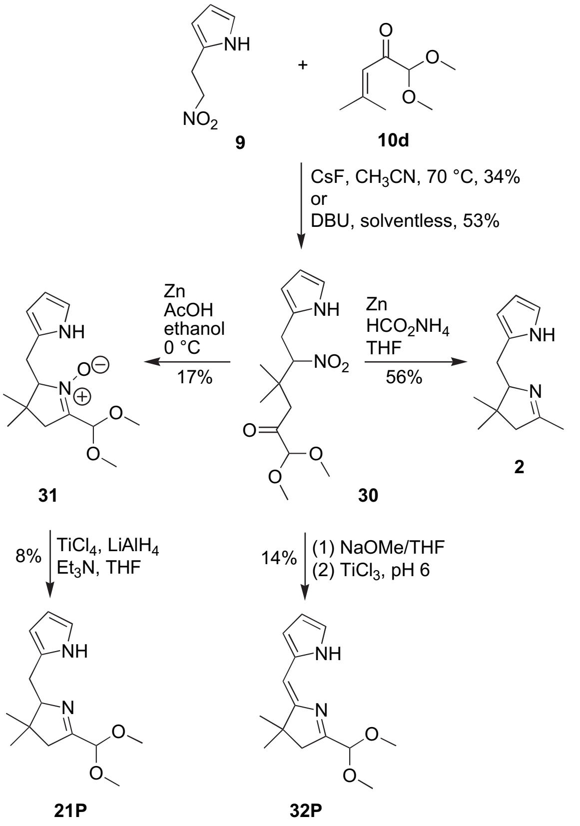
Scheme 6.



Scheme 7.

(**29-Ts**) using $LaCl_3$[44] in methanol in 56% yield. Deoxygenation gave **21P-Ts** in 84% yield. Conversion of **21P-Ts** to **21-Ts** was attempted using established methods for acetal hydrolysis [$MoO_2(acac)_2$ in aqueous acetonitrile;[45] TFA/H_2O (3:1) in CH_2Cl_2[42,46]] but to no avail. ^1H NMR spectroscopy of the crude product obtained with aqueous TFA showed that **21P-Ts** had indeed reacted with water, but with addition of water across the imine rather than hydrolysis of the acetal. In summary, all four approaches to the *N*-*p*-tosyl protected target tetrahydrodipyrrin-carboxaldehyde **21-Ts** failed. On the other hand, removal of the *p*-tosyl protecting group in **21P-Ts** upon basic treatment afforded the target compound **21P**, the dimethyl acetal of **21**.

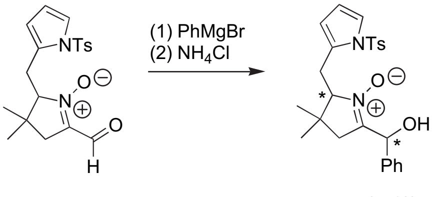
An approach to **21P** without use of *N*-protection is shown in Scheme 8. The Michael addition of 2-(2-nitroethyl)pyrrole (**9**)[18] with α-keto acetal **10d**[15] in the presence of CsF afforded adduct **30** in 34% yield. Alternatively, Michael addition of acetal **10d** with nitroethylpyrrole **9** in the presence of DBU[18] under solventless conditions provided **30** in 53% yield. Reductive cyclization of acetal **30** with Zn/HCO_2NH_4 in THF caused simultaneous reduction of the acetal to the methyl group, affording tetrahydrodipyrrin **2** in 56% yield. To our knowledge, the reduction of the α-acyl acetal, while undesired, also is unprecedented under these conditions. On the other hand, reductive cyclization of **30** in the presence of Zn/acetic acid afforded (17% yield) the *N*-oxide **31**, which upon deoxygenation with Ti(0) gave the tetrahydrodipyrrin-dimethyl acetal **21P**, albeit in very low yield.



Scheme 8.

To compare the reactivity of the tetrahydrodipyrrin-acetal (**21P**) with that of a dihydrodipyrrin-acetal (**32P**), we investigated the synthesis of the latter following the same method employed in the synthesis of dihydrodipyrrin **1**.[10] Jacobi et al. described a related diformyl-dihydrodipyrrin (**B**, Chart 2),[27] but given the difficulties we encountered in pursuit of the 1-formyl-tetrahydrodipyrrin **21**, we elected to prepare an acetal-protected analogue. Thus, reductive cyclization of **30** upon treatment with NaOMe followed by a buffered solution of $TiCl_3$ afforded **32P** (Scheme 8). The yields in both routes to **32P** and **21P** (protected derivatives of **32** and **21**) were quite low, but sufficient material was obtained for subsequent exploratory studies. Such studies indicated that the dihydrodipyrrin-acetal **32P** was more reactive than the tetrahydrodipyrrin-acetal **21P** toward forming the corresponding bacteriochlorin (lacking any β-pyrrole substituents).[47]

2.2.2.3. Tetrahydrodipyrrin-carbinol. The *N*-oxide aldehyde **24-Ts** appeared to be a versatile intermediate given the masked pyrrolic nitrogen, the 'protected' imine, and the free formyl group. To explore conversion of the aldehyde to the secondary carbinol, **24-Ts** was treated with PhMgBr. The resulting diastereomers **33a-Ts** and **33b-Ts** were separated by column chromatography (34% total yield). The carbinols **33a-Ts** and **33b-Ts** were more stable than the corresponding dipyrromethane-based carbinols prepared previously[48] (Scheme 9).



24-Ts

33a-Ts (16%)
33b-Ts (18%)

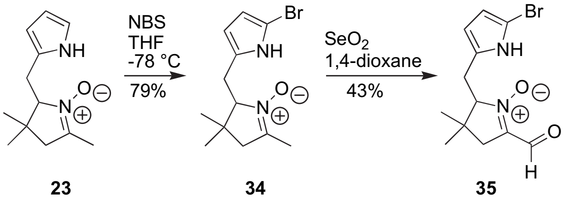
Scheme 9.

In summary, dihydrodipyrrin **32P**, tetrahydrodipyrrin **21P**, and hexahydrodipyrrin **20aP/20bP** each contains one α-carbon and meet the target criteria of E^+/Nu^- reactivity at the 1- and 9-positions.

2.2.3. E^+/E^+ pyrroline–pyrrole units (1 α-carbon).

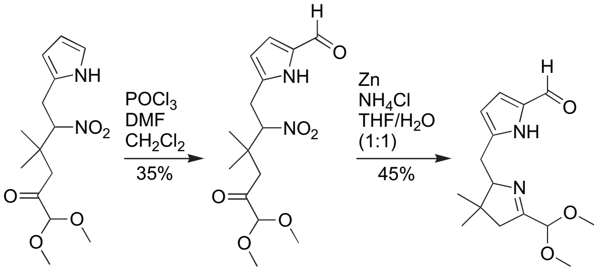
The umpolung analogue of tetrahydrodipyrrin **2** (Nu^-/Nu^-) requires conversion of both nucleophilic units (pyrrole and methyl imine) to electrophilic units. In a previous chlorin synthesis,[10–13] an α-bromo-pyrrole in the Eastern half served as a key electrophilic unit in the carbon–carbon bond-forming cyclization process. Such an α-bromo-pyrrole and an α-formyl-pyrroline are obvious choices for the two electrophiles. However, direct conversion of the methyl imine to the aldehyde (e.g., **2**→**21**) was not viable, prompting examination of the *N*-oxide of tetrahydrodipyrrin **2** (i.e., **23**) as a surrogate for the corresponding conversion.

Treatment of the *N*-oxide **23**[12] with NBS in THF at −78 °C gave selective bromination at the α-pyrrole position, affording bromo *N*-oxide **34** in 79% yield. Oxidation of **34** with SeO_2 gave the aldehyde **35** in 43% yield (Scheme 10). It is noteworthy that the opposite order of bromination and oxidation proved difficult owing to the instability of the pyrrole-*N*-oxide aldehyde. Compound **35** is the *N*-oxide derivative that satisfies the desired E^+/E^+ reactivity pattern and contains one α-carbon.



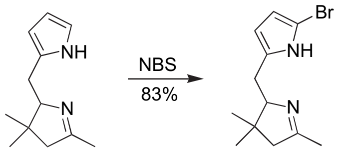
Scheme 10.

2.2.4. E^+/E^+ pyrroline–pyrrole units (2 α-carbons). The nitroacetal **30** was formylated under standard Vilsmeier conditions to afford **36** in 35% yield. The reductive cyclization of **36** in the presence of Zn/NH_4Cl[18] provided tetrahydrodipyrrin **37** in 45% yield (Scheme 11). A small amount of a putative *N*-oxide analogue also was isolated. Compound **37** is the target compound with electrophilic units at both the 1- and 9-positions, and contains two α-carbons. Jacobi et al. prepared a related diformyl-dihydrodipyrrin bearing substituents at both β-pyrrole positions.[27]



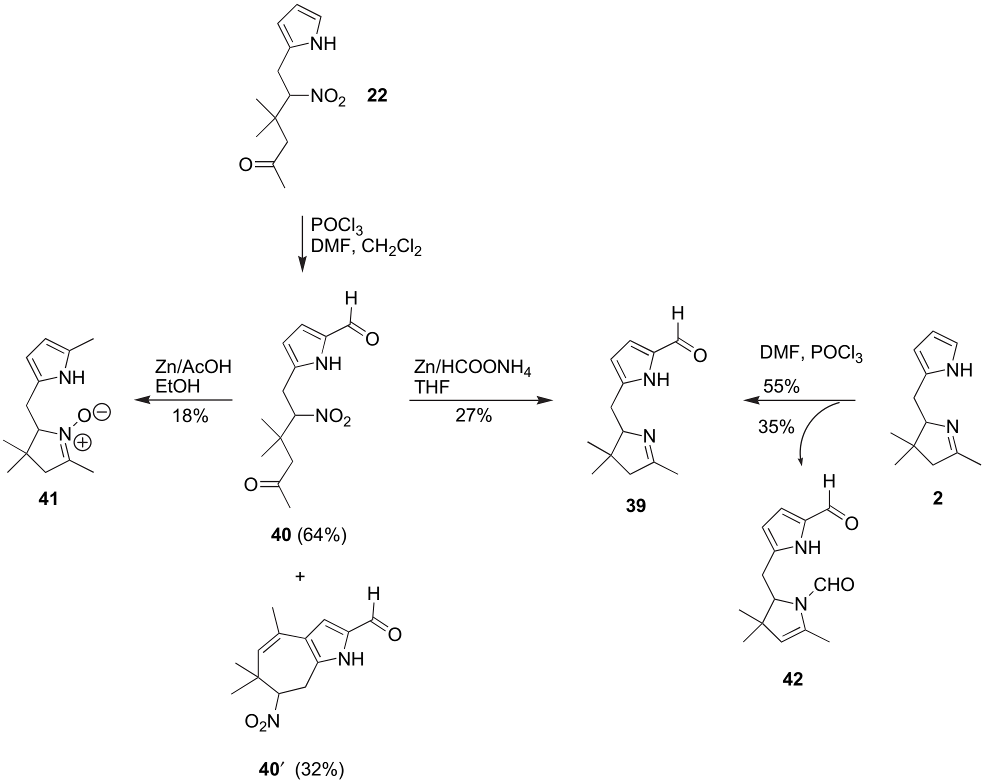
Scheme 11.

2.2.5. Nu^-/E^+ pyrroline–pyrrole units (1 α-carbon). The conversion of the pyrrole unit from a nucleophilic to electrophilic species can be accomplished by bromination. Thus, bromination of tetrahydrodipyrrin **2** with NBS proceeded selectively at the free α-pyrrole position, affording bromotetrahydrodipyrrin **38** in 83% yield (Scheme 12). Compound **38** bears the Nu^-/E^+ reactivity pattern at the 1- and 9-positions and bears one α-carbon.



Scheme 12.

2.2.6. Nu^-/E^+ pyrroline–pyrrole units (2 α-carbons). The tetrahydrodipyrrin bearing an α-pyrroline methyl group and an α-pyrrole carboxaldehyde (**39**) was synthesized according to the route displayed in Scheme 13. Vilsmeier formylation of **22**[18] afforded formyl-nitrohexanone **40** in 64% yield as well as a putative cyclic byproduct (**40′**) in 32% yield. Reductive cyclization of **40** using Zn/HCO_2NH_4



Scheme 13.

in THF afforded **39** in 27% yield. It is interesting to note that use of Zn/AcOH[12] caused reduction of the formyl group and provided 9-methyl substituted *N*-oxide **41**. An alternative route to **39** entailed Vilsmeier formylation of **2**, which afforded **39** in 55% yield together with diformylated **42** in 35% yield. Compound **39** contains the Nu^-/E^+ reactivity pattern at the 1- and 9-positions and contains two α-carbons.

3. Outlook

Three synthetic approaches to hydrodipyrrins that have been developed over the years include (1) stepwise synthesis beginning with a pyrrole-2-carboxaldehyde and proceeding via nitro-aldol condensation, reduction, Michael addition, and metal-mediated reductive cyclization;[16–18,20,22,23,30,49] (2) convergent synthesis utilizing a Wittig reaction of a pyrrole-derived phosphorus ylide and a thione;[21,24–26] and (3) palladium-mediated coupling of a halo-pyrrole with an ethynyl compound followed by cyclization.[27–29,50] The first method, while both the earliest and the most traditional of the three routes, has been exploited herein to gain access to a variety of hydrodipyrrin compounds.

Each new hydrodipyrrin described herein contains one pyrrole and one geminal-dimethyl substituted pyrroline (or pyrrolidine) unit. The α-pyrrole position is either unsubstituted or bears a bromo or formyl substituent; the α-pyrroline position is either unsubstituted or bears a methyl, formyl, acetal, methoxy, or methylsulfanyl substituent; the α-pyrrolidine substituent is a dithiane unit. Hydrodipyrrins bearing distinct groups (methyl, acetal, methoxide, methylsulfanyl, no substituent) at the α-pyrroline position were obtained by Michael addition of 2-(2-nitroethyl)pyrrolic compounds with α,β-unsaturated carbonyl compounds (**10a–d**). The availability of stable tetrahydrodipyrrins with diverse 1- and 9-substituents should facilitate a variety of studies concerning the synthesis of hydroporphyrins.

4. Experimental

4.1. General

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were collected at room temperature in $CDCl_3$ unless noted otherwise. Melting points are uncorrected. Column chromatography was performed with flash silica or alumina (80–200 mesh). The $CHCl_3$ contained 0.8% ethanol. THF was distilled from sodium benzophenone ketyl as required. CH_3CN was distilled from CaH_2 and stored over powdered molecular sieves. NBS was recrystallized (H_2O). Other solvents were used as received.

4.2. Non-commercial compounds

Compounds **2**,[12,18] **7-Boc**,[31] **9**,[18] **10d**,[15] **22**,[18] and **23**[12] were prepared according to literature procedures.

4.3. New synthetic compounds and procedures

4.3.1. 2,3,4,5-Tetrahydro-1,3,3-trimethyl-*N*^{11}-*p*-tosyldipyrrin (2-Ts). Following a procedure for the deoxygenation of *N*-oxides[12] with slight modification, $TiCl_4$ (229 μL, 2.08 mmol) was slowly added with stirring to dry THF (6.0 mL) under argon at 0 °C. The resulting yellow solution was slowly treated with $LiAlH_4$ (56.0 mg, 1.49 mmol). The resulting black mixture was stirred at room temperature for 15 min. Triethylamine (TEA, 1.86 mL, 13.4 mmol) was added. The black mixture was poured into a solution of **23-Ts** (107 mg, 0.297 mmol) in dry THF (60 mL) at 0 °C. The mixture was stirred for 1 h in a water bath (~20 °C), and then water (40 mL) was added. The mixture was filtered. The filtrate was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated. The resulting yellow oil was purified by column chromatography (silica, ethyl acetate) to give a pale yellow oil (76 mg, 75%): ^{1}H NMR δ 0.88 (s, 3H), 1.07 (s, 3H), 1.96–1.99 (m, 3H), 2.27 (AB, ^2J=17.0 Hz, 1H), 2.56 (AB, ^2J=17.0 Hz, 1H), 2.39 (s, 3H), 2.66 (ABX, ^3J=9.8 Hz, ^2J=16.2 Hz, 1H), 2.94 (ABX, ^3J=4.2 Hz, ^2J=16.2 Hz, 1H), 3.72–3.75 (m, 1H), 6.21–6.23 (m, 1H), 6.23–6.25 (m, 1H), 7.27 (d, *J*=8.4 Hz, 2H), 7.28–7.29 (m, 1H), 7.65 (d, *J*=8.4 Hz, 2H); ^{13}C NMR δ 20.7, 21.8, 22.9, 27.3, 28.3, 42.4, 54.8, 78.2, 111.9, 113.7, 122.4, 127.0, 130.1, 134.3, 136.7, 144.9, 174.7; FABMS obsd 345.1649, calcd 345.1637 $[(M+H)^+$, $M=C_{19}H_{24}N_2O_2S]$. Anal. Calcd for $C_{19}H_{24}N_2O_2S$: C, 66.25; H, 7.02; N, 8.13. Found: C, 65.93; H, 6.93; N, 8.00.

4.3.2. 2,3,4,5-Tetrahydro-3,3-dimethyldipyrrin (6). Following a general procedure,[11] a solution of **6-Boc** (299 mg, 1.08 mmol) in anhydrous THF (4.32 mL) under argon at room temperature was treated with methanolic NaOMe (1.50 mL, prepared by dissolving 373 mg of NaOMe in 2.00 mL of MeOH). After 25 min, the reaction was quenched by the addition of a mixture of hexanes and water (20 mL, 1:1). The mixture was extracted with ethyl acetate. The organic extract was washed (water and brine), dried (Na_2SO_4), and chromatographed [alumina, hexanes/ethyl acetate (3:1)] to give a pale yellow oil (64 mg, 34%): IR 3380, 2958 cm^{-1}; ^{1}H NMR δ 0.95 (s, 3H), 1.13 (s, 3H), 2.39–2.41 (m, 2H), 2.60 (ABX, ^3J=11.6 Hz, ^2J=14.8 Hz, 1H), 2.82 (ABX, ^3J=3.2 Hz, ^2J=14.8 Hz, 1H), 3.63–3.69 (m, 1H), 5.95–5.97 (m, 1H), 6.10–6.12 (m, 1H), 6.69–6.71 (m, 1H), 7.63–7.65 (m, 1H), 9.52–9.68 (br s, 1H); ^{13}C NMR δ 23.0, 27.4, 28.0, 40.3, 52.5, 80.9, 105.5, 107.5, 116.7, 131.5, 166.7; EIMS obsd 176.1305, calcd 176.1313 ($C_{11}H_{16}N_2$).

4.3.3. *N*^{11}-*tert*-Butoxycarbonyl-3,3-dimethyl-2,3,4,5-tetrahydrodipyrrin (6-Boc). Following a general procedure,[12] $TiCl_4$ (769 μL, 7.00 mmol) was slowly added with stirring to dry THF (25.0 mL) under argon at 0 °C. The resulting yellow solution was slowly treated with $LiAlH_4$ (190 mg, 5.00 mmol). The resulting black mixture was stirred at room temperature for 25 min. TEA (6.27 mL, 45.0 mmol) was added. The resulting black mixture was stirred for 10 min at room temperature, and then cooled at 0 °C. The black mixture was slowly poured into a solution of **12-Boc** (292 mg, 1.00 mmol) in dry THF (15.0 mL) at 0 °C. The mixture was stirred for 1 h at room temperature, and then water (10 mL) was added. The mixture was filtered. The filtrate was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed (silica, ethyl acetate) to give a pale yellow oil (112 mg, 41%): IR 2958, 1740, 1333, 1126 cm^{-1}; ^{1}H NMR δ 0.97 (s, 3H), 1.14 (s, 3H), 1.58 (s, 9H), 2.39–2.41 (m, 2H), 2.88

(ABX, ^3J=10.4 Hz, ^2J=15.8 Hz, 1H), 3.15 (ABX, ^3J=3.8 Hz, ^2J=15.8 Hz, 1H), 3.77–3.83 (m, 1H), 6.10–6.12 (m, 1H), 6.17–6.18 (m, 1H), 7.19–7.21 (m, 1H), 7.61–7.63 (m, 1H); ^{13}C NMR δ 23.0, 27.2, 28.3, 29.7, 40.7, 52.8, 78.6, 83.2, 110.4, 112.5, 121.1, 134.6, 149.8, 166.7; FABMS obsd 277.1917, calcd 277.1916 [(M+H)$^+$, M=$C_{16}H_{24}N_2O_2$].

4.3.4. 3,3-Dimethyl-2,3,4,5-tetrahydro-*N*^{11}-*p*-tosyldipyrrin (6-Ts). Following a procedure for the deoxygenation of *N*-oxides[12] with slight modification, $TiCl_4$ (3.18 mL, 28.9 mmol) was slowly added with stirring to dry THF (100 mL) under argon at 0 °C. The resulting yellow solution was slowly treated with $LiAlH_4$ (784 mg, 20.7 mmol). The resulting black mixture was stirred at room temperature for 15 min. TEA (25.9 mL, 186 mmol) was added. The black mixture was poured into a solution of **12-Ts** (1.43 g, 4.13 mmol) in dry THF (60 mL) at 0 °C. The mixture was stirred for 1 h in a water bath (~20 °C), and then water (40 mL) was added. The mixture was filtered. The filtrate was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed (silica, ethyl acetate) to give a pale yellow oil, which upon cooling gave a white solid (635 mg, 47%): mp 80–82 °C; ^{1}H NMR δ 0.89 (s, 3H), 1.12 (s, 3H), 2.36–2.37 (m, 2H), 2.39 (s, 3H), 2.62 (ABX, ^3J=10.6 Hz, ^2J=16.2 Hz, 1H), 2.98 (ABX, ^3J=3.8 Hz, ^2J=16.2 Hz, 1H), 3.73–3.79 (m, 1H), 6.22–6.25 (m, 2H), 7.27 (d, J=8.4 Hz, 2H), 7.28–7.31 (m, 1H), 7.56–7.58 (m, 1H), 7.63 (d, J=8.4 Hz, 2H); ^{13}C NMR δ 21.8, 23.0, 27.3, 28.3, 40.7, 52.7, 78.6, 112.0, 113.9, 122.6, 126.9, 130.2, 134.1, 136.8, 144.9, 166.9; FABMS obsd 331.1493, calcd 331.1480 [(M+H)$^+$, M=$C_{18}H_{22}N_2O_2S$].

4.3.5. *N*-*p*-Tosylpyrrole-2-carboxaldehyde (7-Ts).[37] Following a general procedure,[35] a mixture of **7** (4.76 g, 50.0 mmol) and tetrabutylammonium hydrogen sulfate (1.70 g, 5.00 mmol) was added to aqueous NaOH [9.00 g (225 mmol) of NaOH in 30 mL of water]. The mixture was stirred for 10 min. *p*-Toluenesulfonyl chloride (10.5 g, 55.0 mmol) in CH_2Cl_2 (10 mL) was added rapidly. The reaction mixture was stirred for 5 h, then water (200 mL) and brine (100 mL) were added. The mixture was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), concentrated, and chromatographed (silica, CH_2Cl_2) to give a light pink solid (10.7 g, 86%): mp 94–95 °C (lit.[37] mp 94–96 °C); ^{1}H NMR δ 2.42 (s, 3H), 6.39–6.41 (m, 1H), 7.15–7.16 (m, 1H), 7.32 (d, J=8.6 Hz, 2H), 7.61–7.63 (m, 1H), 7.80 (d, J=8.6 Hz, 2H), 9.98 (s, 1H); ^{13}C NMR δ 21.9, 112.6, 124.6, 127.7, 129.6, 130.3, 133.7, 135.4, 146.2, 179.2. Anal. Calcd for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 58.03; H, 4.62; N, 5.64.

4.3.6. *N*-*tert*-Butoxycarbonyl-2-(*trans*-2-nitrovinyl)pyrrole (8-Boc). Following a general procedure,[10] a solution of **7-Boc** (772 mg, 3.70 mmol) in distilled methanol (11.0 mL) was treated with nitromethane (599 µL, 11.1 mmol), sodium acetate (334 mg, 4.07 mmol), and methylamine hydrochloride (275 mg, 4.07 mmol). The mixture was stirred at room temperature for 21 h under argon. The methanol was removed in vacuo without heating to give a yellow solid. The solid was dissolved in CH_2Cl_2 (100 mL), and the resulting solution was washed with water. The organic extract was dried (Na_2SO_4), concentrated, and chromatographed (silica, CH_2Cl_2) to give a yellow solid (562 mg, 64%): mp 123–124 °C; IR 2965, 1748, 1504, 1368, 1331, 1123 cm^{-1}; ^{1}H NMR δ 1.65 (s, 9H), 6.29–6.31 (m, 1H), 6.82–6.83 (m, 1H), 7.48 (d, J=13.6 Hz, 1H), 7.53–7.54 (m, 1H), 8.76 (d, J=13.6 Hz, 1H); ^{13}C NMR δ 28.2, 86.1, 112.4, 118.1, 126.3, 127.7, 130.1, 135.2, 148.7; FABMS obsd 239.1035, calcd 239.1032 [(M+H)$^+$, M=$C_{11}H_{14}N_2O_4$]. Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.40; H, 6.01; N, 11.71.

4.3.7. 2-(*trans*-2-Nitrovinyl)-*N*-*p*-tosylpyrrole (8-Ts). Following a general procedure,[10] a solution of **7-Ts** (17.3 g, 69.4 mmol) in distilled methanol (300 mL) was treated with nitromethane (11.2 mL, 208 mmol), sodium acetate (6.26 g, 76.3 mmol), and methylamine hydrochloride (5.15 g, 76.3 mmol). The mixture was stirred at room temperature for 38 h under argon. The methanol was removed in vacuo without heating to give a yellow solid. The solid was dissolved in CH_2Cl_2 (150 mL), and the resulting solution was washed with water. The organic extract was dried (Mg_2SO_4), concentrated, and chromatographed (silica, CH_2Cl_2) to give a yellow solid (18.3 g, 90%): mp 153–154 °C; ^{1}H NMR (300 MHz) δ 2.42 (s, 3H), 6.39–6.41 (m, 1H), 6.81–6.83 (m, 1H), 7.33 (d, J=8.1 Hz, 2H), 7.36 (d, J=13.5 Hz, 1H), 7.61–7.63 (m, 1H), 7.74 (d, J=8.1 Hz, 2H), 8.51 (d, J=13.5 Hz, 1H); ^{13}C NMR δ 21.6, 113.3, 118.6, 125.5, 126.9, 127.0, 128.3, 130.4, 135.0, 135.6, 146.1. Anal. Calcd for $C_{13}H_{12}N_2O_4S$: C, 53.42; H, 4.14; N, 9.58. Found: C, 53.44; H, 4.17; N, 9.53.

4.3.8. *N*-*tert*-Butoxycarbonyl-2-(2-nitroethyl)pyrrole (9-Boc). Following a general procedure,[11] a solution of **8-Boc** (490 mg, 2.06 mmol) in DMF/methanol (35.0 mL, 1:2) at 0 °C was treated with sodium borohydride (117 mg, 3.09 mmol). The reaction mixture was stirred for 15 min. Water (30 mL) was added followed by acetic acid (one drop). The mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/CH_2Cl_2 (1:4)] to give a pale yellow oil (258 mg, 52%): IR 2980, 1736 cm^{-1}; ^{1}H NMR δ 1.60 (s, 9H), 3.57 (t, J=7.0 Hz, 2H), 4.66 (t, J=7.0 Hz, 2H), 6.05–6.07 (m, 1H), 6.07–6.09 (m, 1H), 7.19–7.21 (m, 1H); ^{13}C NMR δ 27.1, 28.2, 75.0, 84.4, 110.5, 114.0, 122.2, 129.2, 149.5; FABMS obsd 240.1126, calcd 240.1110 ($C_{11}H_{16}N_2O_4$).

4.3.9. One-flask synthesis of *N*-*tert*-butoxycarbonyl-2-(2-nitroethyl)pyrrole (9-Boc). Following a general procedure,[13] a solution of **7-Boc** (3.62 g, 18.5 mmol) in distilled methanol (62.0 mL) was treated with nitromethane (3.00 mL, 55.6 mmol), sodium acetate (1.67 g, 20.4 mmol), and methylamine hydrochloride (1.37 g, 20.4 mmol). Stirring at room temperature for 16 h under argon afforded a yellow mixture. DMF (100 mL) and methanol (138 mL) were added to the reaction mixture. Sodium borohydride (910 mg, 24.1 mmol) was added rapidly at 0 °C. The reaction mixture was stirred at room temperature for 20 min. The mixture was neutralized with acetic acid (~0.5 mL) and then concentrated. The resulting residue was dissolved in CH_2Cl_2 (100 mL) and washed with water. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/$CHCl_3$ (1:4)] to give a pale yellow oil (2.74 g, 61%). The characterization data were identical with those from above.

4.3.10. 2-(2-Nitroethyl)-*N*-*p*-tosylpyrrole (9-Ts). Following a general procedure,[10] a solution of **8-Ts** (5.30 g, 18.1 mmol) in dry THF/methanol (180 mL, 19:1) at 0 °C was treated with sodium borohydride (1.71 g, 45.3 mmol) in portions. The mixture was stirred for 50 min, neutralized with acetic acid (~2 mL), and filtered. The filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (150 mL) and washed with water. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/CH_2Cl_2 (3:7)] to give a light yellow solid (1.64 g, 31%): mp 95–96 °C; ^{1}H NMR δ 2.42 (s, 3H), 3.41 (t, J=6.8 Hz, 2H), 4.61 (t, J=6.8 Hz, 2H), 6.09–6.11 (m, 1H), 6.21–6.23 (m, 1H), 7.30–7.32 (m, 1H), 7.32 (d, J=8.4 Hz, 2H), 7.65 (d, J=8.4 Hz, 2H); ^{13}C NMR δ 21.6, 25.4, 74.4, 111.8, 114.7, 123.6, 126.5, 128.4, 130.2, 135.8, 145.3. Anal. Calcd for $C_{13}H_{14}N_2O_4S$: C, 53.05; H, 4.79; N, 9.52. Found: C, 53.08; H, 4.82; N, 9.43.

4.3.11. One-flask synthesis of 2-(2-nitroethyl)-*N*-*p*-tosylpyrrole (9-Ts). Following a general procedure,[13] a solution of **7-Ts** (10.9 g, 43.7 mmol) in distilled methanol (250 mL) was treated with nitromethane (7.07 mL, 131 mmol), sodium acetate (4.30 g, 52.4 mmol), and methylamine hydrochloride (3.54 g, 52.4 mmol). Stirring at room temperature for 40 h under argon afforded a yellow mixture. DMF (200 mL) and methanol (250 mL) were added to the reaction mixture. Sodium borohydride (1.98 g, 52.4 mmol) was added rapidly at 0 °C. The reaction mixture was stirred at room temperature for 20 min, neutralized with acetic acid (~2 mL), and concentrated. The mixture was dissolved in CH_2Cl_2 (100 mL) and washed with water. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed [silica, CH_2Cl_2/hexanes (7:3)] to give a light yellow solid (7.00 g, 55%). The characterization data were identical with those from above.

4.3.12. 5-(*N*-*tert*-Butoxycarbonyl-2-pyrrolyl)-3,3-dimethyl-4-nitro-1-pentanal (11-Boc). A mixture of **9-Boc** (2.50 g, 10.4 mmol) and 3-methyl-2-butenal (**10a**) (10.0 mL, 104 mmol, 10.0 mol equiv) in dry acetonitrile (10.4 mL) was treated with CsF (4.74 g, 31.2 mmol, 3.00 mol equiv, freshly dried under vacuum for 1 h and purged with argon). The mixture was stirred at room temperature for 2.5 h, whereupon the reaction was deemed to be complete by TLC. The reaction mixture was filtered through alumina (~5 cm). The filtrate was concentrated and chromatographed [silica, hexanes/ethyl acetate (3:1)] to give a pale yellow oil, which upon cooling gave a light brown solid (1.22 g, 36%): mp 73–75 °C; IR 2978, 1737, 1550, 1371, 1324, 1126 cm^{-1}; ^{1}H NMR δ 1.24 (s, 3H), 1.29 (s, 3H), 1.59 (s, 9H), 2.49–2.61 (m, 2H), 3.38 (ABX, ^3J=11.6 Hz, ^2J=15.2 Hz, 1H), 3.58 (ABX, ^3J=2.0 Hz, ^2J=15.2 Hz, 1H), 4.92 (ABX, ^3J=2.0 Hz, ^3J=11.6 Hz, 1H), 5.99–6.00 (m, 1H), 6.02–6.04 (m, 1H), 7.13–7.15 (m, 1H), 9.83–9.85 (m, 1H); ^{13}C NMR δ 24.1, 24.3, 28.1, 28.2, 36.8, 51.7, 84.2, 95.6, 110.5, 114.3, 122.1, 129.3, 149.5, 200.7; FABMS obsd 325.1759, calcd 325.1763 [$(M+H)^+$, $M=C_{16}H_{24}N_2O_5$]. Anal. Calcd for $C_{16}H_{24}N_2O_5$: C, 59.24; H, 7.46; N, 8.64. Found: C, 59.38; H, 7.46; N, 8.47.

4.3.13. 3,3-Dimethyl-4-nitro-5-(*N*-*p*-tosyl-2-pyrrolyl)-1-pentanal (11-Ts). Following a general procedure,[13] CsF (3.40 g, 22.4 mmol, 3.00 mol equiv, freshly dried by heating to 100 °C under vacuum for 1 h and then cooled to room temperature under argon) was placed in a flask under argon. A mixture of **9-Ts** (2.20 g, 7.47 mmol) and 3-methyl-2-butenal (**10a**) (7.21 mL, 74.7 mmol, 10.0 mol equiv) in dry acetonitrile (75 mL) was cannulated into the flask containing CsF. The mixture was heated at 55 °C for 90 min, whereupon the reaction was deemed to be complete by TLC. The reaction mixture was filtered through a pad of silica (ethyl acetate). The filtrate was concentrated and chromatographed [silica, hexanes/ethyl acetate (3:1)] to give a pale yellow oil (1.96 g, 69%): ^{1}H NMR (300 MHz) δ 1.22 (s, 3H), 1.27 (s, 3H), 2.43 (s, 3H), 2.40–2.60 (m, 2H), 3.23 (ABX, ^3J=2.2 Hz, ^2J=15.4 Hz, 1H), 3.34 (ABX, ^3J=11.4 Hz, ^2J=15.4 Hz, 1H), 4.92 (ABX, ^3J=2.2 Hz, ^3J=11.4 Hz, 1H), 6.02–6.06 (m, 1H), 6.17–6.20 (m, 1H), 7.26–7.28 (m, 1H), 7.32 (d, J=8.0 Hz, 2H), 7.58 (d, J=8.0 Hz, 2H), 9.80–9.82 (m, 1H); ^{13}C NMR δ 21.9, 24.2, 24.5, 27.0, 36.9, 51.5, 95.6, 112.4, 115.7, 124.2, 126.5, 128.8, 130.5, 136.3, 145.6, 200.4. Anal. Calcd for $C_{18}H_{22}N_2O_5S$: C, 57.13; H, 5.86; N, 7.40. Found: C, 57.12; H, 5.84; N, 7.20.

4.3.14. *N*^{11}-*tert*-Butoxycarbonyl-2,3,4,5-tetrahydro-3,3-dimethyldipyrrin *N*^{10}-oxide (12-Boc). Following a general procedure,[12] a vigorously stirred solution of **11-Boc** (364 mg, 1.12 mmol) in 5.50 mL of acetic acid and 5.50 mL of ethanol at 0 °C was treated slowly with zinc dust (1.83 g, 28.0 mmol) in small portions for 5 min. The reaction mixture was stirred at 0 °C for 15 min and then filtered through Celite. The filtrate was concentrated under high vacuum. The resulting residue was dissolved in CH_2Cl_2 (50 mL), affording a solution that was washed with aqueous sodium carbonate (20%, 30 mL), dried (Na_2SO_4), and concentrated. The resulting light brown oil was purified by column chromatography [silica; $CH_2Cl_2 \rightarrow$ ethyl acetate $\rightarrow CH_2Cl_2$/methanol (9:1)] to give a light brown oil (**6-Boc**, 49 mg, 16%) and the title compound as a light brown solid (127 mg, 39%). Data for the title compound: mp 116–118 °C; IR 3393, 2974, 1737, 1334, 1126 cm^{-1}; ^{1}H NMR δ 1.07 (s, 3H), 1.12 (s, 3H), 1.59 (s, 9H), 2.36–2.39 (m, 2H), 3.22 (ABX, ^3J=9.6 Hz, ^2J=15.6 Hz, 1H), 3.72 (ABX, ^3J=5.2 Hz, ^2J=15.6 Hz, 1H), 4.05–4.10 (m, 1H), 6.07–6.11 (m, 2H), 6.84–6.86 (m, 1H), 7.19–7.21 (m, 1H); ^{13}C NMR δ 23.0, 26.5, 28.2, 28.3, 39.6, 42.6, 79.2, 83.9, 110.2, 113.6, 121.6, 131.3, 132.8, 149.6; FABMS obsd 293.1875, calcd 293.1865 [$(M+H)^+$, $M=C_{16}H_{24}N_2O_3$].

4.3.15. 2,3,4,5-Tetrahydro-3,3-dimethyl-*N*^{11}-*p*-tosyldipyrrin *N*^{10}-oxide (12-Ts). Following a general procedure,[12] a vigorously stirred solution of **11-Ts** (1.94 g, 5.13 mmol) in a solution of acetic acid (24.0 mL) and ethanol (24.0 mL) at 0 °C was treated slowly with zinc dust (8.39 g, 128 mmol) in small portions for 5 min. The reaction mixture was stirred at 0 °C for 15 min. The mixture was filtered through Celite. The filtrate was concentrated under high vacuum. The resulting oil was purified by column chromatography [silica, CH_2Cl_2/ethyl acetate (1:1) $\rightarrow CH_2Cl_2$/methanol (9:1)] to afford a brown oil (796 mg, 45%): ^{1}H NMR δ 1.02 (s, 3H), 1.12 (s, 3H), 2.38–2.41 (m, 2H), 2.40 (s, 3H), 3.17 (ABX, ^3J=10.6 Hz, ^2J=16.2 Hz, 1H), 3.43 (ABX, ^3J=3.8 Hz, ^2J=16.2 Hz, 1H), 4.05–4.11 (m, 1H), 6.09–6.11 (m, 1H), 6.20–6.23 (m, 1H), 6.84–6.87 (m, 1H), 7.29 (d, J=8.4 Hz, 2H), 7.30–7.33 (m, 1H), 7.68 (d, J=8.4 Hz, 2H); ^{13}C NMR δ 21.8, 23.3, 24.9, 29.0, 39.4, 42.7, 79.8, 111.8, 114.3, 123.2, 127.1, 130.3, 130.8, 133.3, 136.0, 145.3; FABMS obsd 347.1420, calcd 347.1429 [(M+H)$^+$, M=$C_{18}H_{22}N_2O_3S$].

4.3.16. 2,3,4,5-Tetrahydro-3,3-dimethyldipyrrin N^{10}-oxide (13). Following a general procedure,[11] a solution of **12-Boc** (413 mg, 1.41 mmol) in anhydrous THF (9.0 mL) under argon at room temperature was treated with methanolic NaOMe (1.40 mL of a solution prepared by dissolving 486 mg of NaOMe in 2.00 mL of MeOH). After 25 min, the reaction was quenched by the addition of a mixture of hexanes and water (40 mL, 1:1). The mixture was extracted with ethyl acetate. The organic extract was washed (water and brine), dried (Na_2SO_4), and chromatographed (silica, ethyl acetate) to give a light brown oil (106 mg, 39%): IR 3255, 2962, 1590, 1236 cm^{-1}; ^{1}H NMR δ 1.15 (s, 3H), 1.22 (s, 3H), 2.29–2.48 (m, 2H), 2.99 (ABX, ^3J=3.0 Hz, ^2J=15.8 Hz, 1H), 3.07 (ABX, ^3J=7.4 Hz, ^2J=15.8 Hz, 1H), 3.85–3.89 (m, 1H), 5.93–5.96 (m, 1H), 6.05–6.09 (m, 1H), 6.70–6.72 (m, 1H), 6.93–6.95 (m, 1H), 10.30–10.46 (br s, 1H); ^{13}C NMR δ 23.0, 25.6, 27.8, 40.2, 42.6, 81.6, 106.5, 107.5, 117.8, 128.7, 135.5; EIMS obsd 192.1265, calcd 192.1263 ($C_{11}H_{16}N_2O$).

4.3.17. 2,3,4,5-Tetrahydro-1-methoxy-3,3-dimethyldipyrrin (14). Following a general procedure,[23] a mixture of **17** (0.129 g, 0.670 mmol) and trimethyloxonium tetrafluoroborate (0.109 g, 0.740 mmol) in CH_2Cl_2 (2.2 mL) was purged with argon for 10 min. A sample of *N*,*N*-diisopropylethylamine (DIEA, 0.130 mL, 0.740 mmol) was added. The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed (water and brine), dried (Na_2SO_4), and concentrated to afford a brown oil. The crude product was chromatographed [silica, ethyl acetate] to afford a brown solid (70 mg, 50%). A light pink byproduct also was isolated and identified as 2,3,4,5-tetrahydro-3,3,10-trimethyldipyrrin-1(10*H*)-one (**15**) (14 mg, 10%). Data for **14**: mp 85–88 °C; ^{1}H NMR δ 1.02 (s, 3H), 1.14 (s, 3H), 2.25 (AB, ^2J=16.4 Hz, 1H), 2.41 (AB, ^2J=16.4 Hz, 1H), 2.58 (ABX, ^3J=11.6 Hz, ^2J=14.8 Hz, 1H), 2.77 (ABX, ^3J=2.6 Hz, ^2J=14.8 Hz, 1H), 3.57–3.61 (m, 1H), 3.96 (s, 3H), 5.91–5.96 (m, 1H), 6.10–6.12 (m, 1H), 6.69–6.76 (m, 1H), 9.67–9.95 (br s, 1H); ^{13}C NMR δ 23.2, 27.6, 28.8, 42.2, 46.7, 55.2, 75.3, 105.4, 107.6, 116.5, 132.0, 172.2; FABMS obsd 207.1498, calcd 207.1497 [(M+H)$^+$, M=$C_{12}H_{18}N_2O$]. Data for **15**: mp 92–95 °C; ^{1}H NMR δ 1.01 (s, 3H), 1.10 (s, 3H), 2.02 (AB, ^2J=16.2 Hz, 1H), 2.22 (AB, ^2J=16.2 Hz, 1H), 2.55 (s, 3H), 2.73 (ABX, ^3J=8.4 Hz, ^2J=14.8 Hz, 1H), 2.90 (ABX, ^3J=5.4 Hz, ^2J=14.8 Hz, 1H), 3.28 (ABX, ^3J=5.4 Hz, ^3J=8.4 Hz, 1H), 5.94–6.10 (m, 1H), 6.12–6.14 (m, 1H), 6.64–6.71 (m, 1H), 8.52–8.61 (br s, 1H); ^{13}C NMR δ 23.0, 28.7, 29.1, 29.3, 37.1, 45.3, 70.4, 107.0, 109.1, 117.0, 128.1, 174.7; FABMS obsd 207.1498, calcd 207.1497 [(M+H)$^+$, M=$C_{12}H_{18}N_2O$]. Anal. Calcd for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.58. Found: C, 69.93; H, 8.86; N, 13.33.

4.3.18. Methyl 3,3-dimethyl-4-nitro-5-(2-pyrroyl)pentanoate (16) via a solventless procedure with DBU. Following a general procedure,[18] a mixture of **9** (0.220 g, 1.57 mmol) and methyl 3,3-dimethylacrylate (0.96 mL, 7.9 mmol, 5.0 mol equiv) was treated with DBU (0.70 mL, 4.7 mmol, 3.0 mol equiv). The reaction mixture was stirred at 65 °C for 16 h under argon. The crude reaction mixture was diluted with ethyl acetate (20 mL) and washed with water and brine. The organic layer was dried (Na_2SO_4) and concentrated. Excess methyl 3,3-dimethylacrylate was removed under high vacuum. The crude product was chromatographed [silica, hexanes/ethyl acetate (3:1)] to afford a dark brown oil (80.0 mg, 20%): ^{1}H NMR δ 1.16 (s, 3H), 1.21 (s, 3H), 2.42 (s, 2H), 3.10 (ABX, ^3J=2.4 Hz, ^2J=15.4 Hz, 1H), 3.37 (ABX, ^3J=11.6 Hz, ^2J=15.4 Hz, 1H), 3.72 (s, 3H), 4.94 (ABX, ^3J=11.6 Hz, ^3J=2.4 Hz, 1H), 5.96–6.02 (m, 1H), 6.10–6.11 (m, 1H), 6.67–6.68 (m, 1H), 8.02–8.22 (br s, 1H); ^{13}C NMR δ 24.0, 24.8, 27.2, 36.8, 43.8, 52.1, 96.0, 107.5, 108.9, 118.1, 126.0, 171.6; FABMS obsd 255.1336, calcd 255.1345 [(M+H)$^+$, M=$C_{12}H_{18}N_2O_4$].

4.3.19. Synthesis of 16 in acetonitrile with DBU. Following a general procedure,[18] a mixture of **9** (4.2 g, 30 mmol) and methyl 3,3-dimethylacrylate (**10b**, 37 mL, 300 mmol, 10 mol equiv) in CH_3CN (75 mL) was treated with DBU (14 mL, 90 mmol, 3.0 mol equiv) under argon. The reaction mixture was stirred at 65 °C for 16 h under argon. The crude reaction mixture was diluted with ethyl acetate (50 mL), washed (water and brine), dried (Na_2SO_4), and concentrated. Excess methyl 3,3-dimethylacrylate was removed under high vacuum. The crude residue was chromatographed [silica, hexanes/ethyl acetate (3:1)] to afford a dark brown oil (1.43 g, 19%). The data (^{1}H NMR, ^{13}C NMR, and FABMS) were consistent with those obtained from samples prepared via the solventless method.

4.3.20. Synthesis of 16 in acetonitrile with CsF. Following a general procedure,[12] CsF (9.11 g, 60.0 mmol, 3.0 mol equiv, freshly dried by heating at 100 °C under vacuum for 1 h and then cooled to room temperature under argon) was placed in a flask. A mixture of **9** (2.80 g, 20.0 mmol) and methyl 3,3-dimethylacrylate (**10b**, 25.0 mL, 200 mol, 10.0 mol equiv) in CH_3CN (100 mL) was transferred by cannula to the flask containing CsF. The reaction mixture was stirred overnight at 65 °C under argon. The reaction mixture was diluted with ethyl acetate (50 mL) and washed (water and brine), dried (Na_2SO_4), and concentrated. Excess methyl 3,3-dimethylacrylate was removed under high vacuum. The crude product was chromatographed [silica, hexanes/ethyl acetate (3:1)] to afford a dark brown oil (0.56 g, 11%). The data (^{1}H NMR, ^{13}C NMR, and FABMS) were consistent with those obtained from samples prepared via the solventless method.

4.3.21. Synthesis of 16 in THF with TBAF. Following a general procedure[23] with slight modification, nitroethylpyrrole **9** (4.20 g, 30.0 mmol) and powdered molecular sieves 4 Å (100 g) were placed in a reaction flask and purged with argon. Methyl 3,3-dimethylacrylate (**10b**, 37.0 mL, 300 mmol, 10.0 mol equiv) and TBAF (66.0 mL, 1 M in THF, ~66 mmol, 2.2 mol equiv) in THF (234 mL) were added. The reaction mixture was stirred overnight at room temperature under argon. The reaction mixture was then filtered through a column (silica, ethyl acetate). The filtrate was concentrated, dissolved in ethyl acetate, washed (water and brine), dried (Na_2SO_4), and concentrated. Excess methyl 3,3-dimethylacrylate was removed under high vacuum. Chromatography [silica, hexanes/ethyl acetate (3:1)] afforded a brown oil (3.25 g, 43%). The data (^{1}H NMR, ^{13}C NMR, and FABMS) were consistent with those obtained from samples prepared via the solventless method.

4.3.22. 2,3,4,5-Tetrahydro-3,3-dimethyldipyrrin-1(10*H*)-one (17) via Zn/HCO_2NH_4. Following a general procedure,[18] a solution of **16** (0.153 g, 0.600 mmol) in ethanol (1.2 mL) was treated with HCO_2NH_4 (0.378 g, 6.00 mmol) and zinc dust (0.589 g, 9.00 mmol). The mixture was stirred overnight at room temperature. The crude reaction mixture was diluted with ethyl acetate and filtered. The filter cake was washed with ethyl acetate. The filtrate was washed (water and brine), dried (Na_2SO_4), and concentrated to give a red oil. Chromatography [silica, hexanes/ethyl acetate/methanol (8:5:2)] afforded a brown solid (10 mg, 9%) and a byproduct identified as 2,3,4,5-tetrahydro-1-hydroxy-3,3-dimethyldipyrrin (**17-OH**) (23 mg, 18%). Data for **17**: mp 92–94 °C; ^{1}H NMR δ 1.12 (s, 3H), 1.16 (s, 3H), 2.15–2.25 (m, 2H), 2.56 (ABX, ^3J=11.2 Hz, ^2J=14.4 Hz, 1H), 2.84 (ABX, ^3J=2.8 Hz, ^2J=14.4 Hz, 1H), 3.48 (ABX, ^3J=2.8 Hz, ^2J=11.2 Hz, 1H), 5.62–5.78 (br s, 1H), 5.94–6.20 (m, 1H), 6.14–6.16 (m, 1H), 6.69–6.71 (m, 1H), 8.10–8.25 (br s, 1H); ^{13}C NMR δ 22.9, 27.6, 29.3, 38.7, 46.3, 64.5, 106.7, 108.9, 117.7, 128.5, 177.2; FABMS obsd 193.1337, calcd 193.1341 [(M+H)$^+$, M=$C_{11}H_{16}N_2O$]. Data for **17-OH**: mp 120–122 °C; ^{1}H NMR δ 1.13 (s, 3H), 1.20 (s, 3H), 1.81 (AB, ^2J=16.4 Hz, 1H), 1.96 (AB, ^2J=16.4 Hz, 1H), 2.96 (ABX, ^3J=3.7 Hz, ^2J=15.6 Hz, 1H), 3.11 (ABX, ^3J=3.7 Hz, ^2J=15.6 Hz, 1H), 3.54–3.69 (m, 1H), 5.95–6.02 (m, 1H), 6.04–6.14 (m, 1H), 6.59–6.72 (m, 1H), 9.02–9.07 (br s, 1H) (the OH proton was not observed); ^{13}C NMR δ 22.7, 26.5, 29.7, 35.1, 43.0, 69.9, 108.05, 108.09, 117.9, 126.9, 170.8; FABMS obsd 209.1291, calcd 209.1290 [(M+H)$^+$, M=$C_{11}H_{16}N_2O_2$].

4.3.23. Synthesis of 17 via Zn/AcOH. Following a general procedure,[12] a solution of **16** (0.255 g, 1.00 mmol) in ethanol (5.0 mL) was treated with AcOH (5.0 mL). The reaction mixture changed immediately from dark brown to dark red. Zinc dust (1.64 g, 25.0 mmol) was added in portions over 5 min. The resulting mixture was stirred overnight at room temperature. The mixture was diluted with ethyl acetate and filtered. The filtrate was neutralized with saturated aqueous $NaHCO_3$, washed (water and brine), dried, and concentrated. The resulting light brown crude mixture was chromatographed [silica, hexanes/ethyl acetate/methanol (8:5:2)]. The first fraction contained the title compound, which was isolated and concentrated to afford light brown crystals (60 mg, 30%). The second fraction was isolated (41 mg) and found to contain a mixture of **17** and **17-OH**. Further chromatography of the second fraction gave **17-OH** as a red-brown solid (20 mg, 10%). The data for **17** and **17-OH** (mp, ^{1}H NMR, ^{13}C NMR, and FABMS) were consistent with those obtained from samples prepared via reduction with Zn/HCO_2NH_4.

4.3.24. Synthesis of 17 via Zn/HCO_2H. Following a general procedure,[32] a solution of **16** (0.101 g, 0.400 mmol) in ethanol (3.6 mL) was treated with formic acid (0.9 mL) and zinc dust (0.65 g, 10 mmol). The resulting mixture was stirred overnight at room temperature. The mixture was diluted with ethyl acetate and then filtered through a sintered glass funnel. The filtered material was washed with ethyl acetate (~20 mL). The filtrate was neutralized with saturated aqueous $NaHCO_3$, washed (water and brine), dried (Na_2SO_4), and concentrated. The crude product was chromatographed [silica, hexanes/ethyl acetate/methanol (8:5:2)] to afford white crystals (35 mg, 45%). The characterization data (mp, ^{1}H NMR, ^{13}C NMR, and FABMS) were consistent with those obtained from samples prepared via reduction with Zn/HCO_2NH_4.

4.3.25. 2,3,4,5-Tetrahydro-3,3-dimethyldipyrrin-1(10*H*)-thione (18). Following a general procedure[24] with slight modification, a mixture of **17** (0.0634 g, 0.330 mmol) and Lawesson's reagent (0.154 g, 0.382 mmol) in anhydrous toluene (14 mL) was refluxed overnight. The reaction mixture was then concentrated and chromatographed [silica, CH_2Cl_2/ethyl acetate (5:3)] to afford a white solid (0.029 g, 43%): mp 105–108 °C; ^{1}H NMR δ 1.09 (s, 3H), 1.24 (s, 3H), 2.63 (ABX, ^3J=11.4 Hz, ^2J=14.8 Hz, 1H), 2.74 (s, 2H), 2.84 (ABX, ^3J=3.3 Hz, ^2J=14.8 Hz, 1H), 3.75 (ABX, ^3J=3.3 Hz, ^3J=11.4 Hz, 1H), 5.98–6.04 (m, 1H), 6.15–6.18 (m, 1H), 6.71–6.73 (m, 1H), 7.50–7.62 (br s, 1H), 8.02–8.18 (br s, 1H); ^{13}C NMR δ 22.4, 26.8, 28.2, 41.3, 58.4, 70.7, 107.0, 109.4, 118.0, 127.3, 204.9; FABMS obsd 209.1103, calcd 209.1112 [(M+H)$^+$, M=$C_{11}H_{16}N_2S$].

4.3.26. 2,3,4,5-Tetrahydro-1-methylsulfanyl-3,3-dimethyldipyrrin (19). Following a reported procedure,[24] a solution of **18** (0.023 g, 0.11 mmol) in THF (3 mL) was treated first with Ag_2CO_3 (0.097 g, 0.35 mmol) and then dropwise with MeI (22 μL, 0.35 mmol). The mixture was stirred at 55 °C for 4 h under argon. The reaction mixture was washed (5% aqueous $NaHCO_3$, water, and brine), dried, and concentrated. Chromatography [silica, hexanes/ethyl acetate (1:1)] afforded a white solid (0.012 g, 49%): mp 112–115 °C; ^{1}H NMR δ 0.98 (s, 3H), 1.15 (s, 3H), 2.41–2.45 (m, 1H), 2.50 (s, 3H), 2.51–2.54 (m, 1H), 2.59–2.66 (m, 1H), 2.77–2.82 (m, 1H), 3.67–3.71 (m, 1H), 5.95–5.99 (m, 1H), 6.12–6.14 (m, 1H), 6.72–6.73 (m, 1H), 9.76–9.84 (br s, 1H); ^{13}C NMR δ 13.8, 22.8, 27.1, 28.2, 43.0, 53.8, 80.3, 105.6, 107.7, 116.7, 131.8, 172.7; FABMS obsd 223.1263, calcd 223.1269 [(M+H)$^+$, M=$C_{12}H_{18}N_2S$].

4.3.27. 1-(1,3-Dithian-2-yl)-1,2,3,4-tetrahydro-3,3-dimethyldipyrromethane (20aP). Following a general procedure,[36] a mixture of **20aP-Ts** (86 mg, 0.19 mmol) in 2-propanol (1.3 mL) and 10 N aqueous NaOH (2.0 mL) was stirred under reflux for 3 days. After cooling to room temperature, the mixture was concentrated at reduced pressure. The resulting residue was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), concentrated, and chromatographed (silica, ethyl acetate) to give a colorless oil (27 mg, 47%): ^{1}H NMR δ 1.03 (s, 3H), 1.04 (s, 3H), 1.69–1.83 (m, 2H), 1.85–1.92 (m, 1H), 2.10–2.16 (m, 1H), 2.20–2.31 (br s, 1H), 2.40–2.49 (m, 1H), 2.67–2.72 (m, 1H), 2.82–2.88 (m, 5H), 3.40–3.47 (m, 1H), 4.10 (d, J=7.2 Hz, 1H), 5.88–5.91 (m, 1H), 6.09–6.11 (m, 1H), 6.69–6.71 (m, 1H), 9.40–9.67 (br s, 1H); ^{13}C NMR δ 24.0, 26.4, 28.3, 30.0, 30.2, 30.3, 41.5, 44.1, 54.8, 59.6, 68.4, 105.5, 107.7, 116.7, 131.6; FABMS obsd 297.1462, calcd 297.1459 [(M+H)$^+$, M=$C_{15}H_{24}N_2S_2$].

4.3.28. 1-(1,3-Dithian-2-yl)-1,2,3,4-tetrahydro-3,3-dimethyldipyrromethane (20bP). Following a general procedure,[36] a mixture of **20bP-Ts** (210 mg, 0.466 mmol) in 2-propanol (3.00 mL) and 5 N aqueous NaOH (2.50 mL) was stirred at reflux for 3 days. After cooling to room temperature, the mixture was concentrated at reduced pressure. The resulting residue was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), concentrated, and chromatographed (silica, ethyl acetate) to give a light brown solid (61 mg, 44%): mp 108–110 °C; ^{1}H NMR δ 0.89 (s, 3H), 1.02 (s, 3H), 1.69 (ABX, ^3J=8.4 Hz, ^2J=12.8 Hz, 1H), 1.84 (ABX, ^3J=7.6 Hz, ^2J=12.8 Hz, 1H), 1.82–1.93 (m, 1H), 2.04–2.17 (m, 2H), 2.41 (ABX, ^3J=10.4 Hz, ^2J=15.4 Hz, 1H), 2.76 (ABX, ^3J=2.8 Hz, ^2J=15.4 Hz, 1H), 2.80–2.88 (m, 4H), 2.95 (ABX, ^3J=2.8 Hz, ^3J=10.4 Hz, 1H), 3.47–3.53 (m, 1H), 4.04 (d, J=7.2 Hz, 1H), 5.90–5.94 (m, 1H), 6.10–6.13 (m, 1H), 6.68–6.71 (m, 1H), 9.15–9.27 (br s, 1H); ^{13}C NMR δ 21.2, 25.8, 26.3, 28.2, 30.1, 42.4, 46.1, 55.0, 58.8, 67.4, 105.5, 108.1, 116.6, 130.7; FABMS obsd 297.1466, calcd 297.1459 [$(M+H)^+$, M=$C_{15}H_{24}N_2S_2$].

4.3.29. 9-(1,3-Dithian-2-yl)-6,7,8,9-tetrahydro-7,7-dimethyl-*N*^{10}-*p*-tosyldipyrromethane (20P-Ts). Following a procedure for organolithium addition to imines,[38] a solution of 1,3-dithiane (919 mg, 7.64 mmol) in dry THF (8 mL) at −20 °C (salt ice bath) was treated with *n*-butyl lithium (3.10 mL, 2.5 M in hexane, 7.64 mmol) followed by stirring for 30 min at −20 °C. The flask was then cooled to −78 °C. A sample of **6-Ts** (630 mg, 1.91 mmol) was added, and the mixture was stirred for 1 h at −20 °C. The flask was placed in a bath at −78 °C and stirred for 5 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl (20 mL). The mixture was extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4) and concentrated. TLC analysis [silica, hexanes/ethyl acetate (9:1)] showed two components with R_f=0.67 (**20aP-Ts**, minor) and R_f=0.47 (**20b-Ts**, major). Column chromatography [silica, hexanes/ethyl acetate (7:3)] afforded each isomer as a light yellow oil. Each oil solidified upon cooling to give a light brown solid (**20aP-Ts**, 98 mg, 11%; **20bP-Ts**, 151 mg, 18%). Data for **20aP-Ts**: mp 103–105 °C; ^{1}H NMR δ 0.97 (s, 3H), 1.02 (s, 3H), 1.59 (ABX, ^3J=8.0 Hz, ^2J=13.2 Hz, 1H), 1.79 (ABX, ^3J=8.4 Hz, ^2J=13.2 Hz, 1H), 1.84–1.93 (m, 2H), 2.03–2.08 (m, 1H), 2.40 (s, 3H), 2.48–2.55 (m, 1H), 2.77–2.95 (m, 6H), 3.21–3.27 (m, 1H), 3.90 (d, J=8.4 Hz, 1H), 6.11–6.13 (m, 1H), 6.18–6.20 (m, 1H), 7.25–7.28 (m, 1H), 7.27 (d, J=8.4 Hz, 2H), 7.60 (d, J=8.4 Hz, 2H); ^{13}C NMR δ 21.6, 24.5, 25.9, 27.7, 29.0, 29.3, 29.5, 39.1, 45.2, 53.2, 58.1, 66.2, 111.6, 113.5, 122.8, 126.5, 130.0, 133.9, 136.6, 144.7; FABMS obsd 451.1540, calcd 451.1548 [$(M+H)^+$, M=$C_{22}H_{30}N_2O_2S_3$]. Anal. Calcd for $C_{22}H_{30}N_2O_2S_3$: C, 58.63; H, 6.71; N, 6.22. Found: C, 58.42; H, 6.75; N, 5.96. Data for **20bP-Ts**: mp 126–128 °C; ^{1}H NMR δ 0.90 (s, 3H), 1.00 (s, 3H), 1.65 (ABX, ^3J=8.6 Hz, ^2J=12.8 Hz, 1H), 1.77 (ABX, ^3J=7.2 Hz, ^2J=12.8 Hz, 1H), 1.83–1.90 (m, 1H), 1.93–2.01 (br s, 1H), 2.03–2.10 (m, 1H), 2.39 (s, 3H), 2.39–2.46 (m, 1H), 2.71–2.86 (m, 5H), 3.02–3.05 (m, 1H), 3.42–3.48 (m, 1H), 3.90 (d, J=7.2 Hz, 1H), 6.15–6.18 (m, 1H), 6.18–6.21 (m, 1H), 7.25–7.27 (m, 1H), 7.27 (d, J=8.4 Hz, 2H), 7.61 (d, J=8.4 Hz, 2H); ^{13}C NMR δ 21.5, 21.6, 25.9, 26.0, 28.8, 29.3, 29.4, 41.2, 45.5, 54.2, 57.7, 64.8, 111.6, 113.1, 122.5, 126.6, 129.9, 133.7, 136.5, 144.7; FABMS obsd 451.1556, calcd 451.1548 [$(M+H)^+$, M=$C_{22}H_{30}N_2O_2S_3$].

4.3.30. 1-(Dimethoxymethyl)-2,3,4,5-tetrahydro-3,3-dimethyldipyrrin (21P). Following a general procedure,[36] a mixture of **21P-Ts** (491 mg, 1.21 mmol) in 2-propanol (12 mL) and 5 N aqueous NaOH (12 mL) was stirred under reflux for 10 days. After cooling to room temperature, water (50 mL) was added to the mixture. The mixture was extracted with ethyl acetate. The organic extract was washed with water, dried (Na_2SO_4), concentrated, and chromatographed [silica, CH_2Cl_2/ethyl acetate (4:1)] to give a colorless oil (131 mg, 43%): ^{1}H NMR δ 0.96 (s, 3H), 1.12 (s, 3H), 2.39–2.51 (m, 2H), 2.64 (ABX, ^3J=11.4 Hz, ^2J=14.6 Hz, 1H), 2.83 (ABX, ^3J=3.2 Hz, ^2J=14.6 Hz, 1H), 3.43 (s, 3H), 3.44 (s, 3H), 3.70–3.76 (m, 1H), 4.81 (s, 1H), 5.93–5.97 (m, 1H), 6.09–6.12 (m, 1H), 6.69–6.73 (m, 1H), 9.53–9.63 (br s, 1H); ^{13}C NMR δ 22.9, 27.4, 28.1, 41.4, 48.8, 54.7, 54.8, 80.6, 103.1, 105.6, 107.6, 116.8, 131.4, 174.2; FABMS obsd 251.1753, calcd 251.1760 [$(M+H)^+$, M=$C_{14}H_{22}N_2O_2$].

4.3.31. 1-(Dimethoxymethyl)-2,3,4,5-tetrahydro-3,3-dimethyldipyrrin (21P) from 31. Following a general procedure,[12] a sample of $TiCl_4$ (86 μL, 0.79 mmol) was slowly added with stirring to dry THF (2.0 mL) under argon at 0 °C. The resulting yellow solution was slowly treated with $LiAlH_4$ (20 mg, 0.53 mmol). The resulting black mixture was stirred at room temperature for 15 min. TEA (0.690 mL, 4.95 mmol) was added. The resulting black mixture was stirred for 2 min at room temperature. The black mixture was slowly poured into a solution of **31** (30 mg, 0.11 mmol) in dry THF (1.5 mL) at 0 °C. The mixture was stirred for 30 min at room temperature, and then water (4 mL) was added. The resulting mixture was extracted with CH_2Cl_2 and ethyl acetate. The organic extract was washed with water, dried (Na_2SO_4), and chromatographed [silica, CH_2Cl_2/ethyl acetate (4:1)] to give a colorless oil (2.2 mg, 8%). The characterization data were identical with those described above.

4.3.32. 1-(Dimethoxymethyl)-2,3,4,5-tetrahydro-3,3-dimethyl-*N*^{11}-*p*-tosyldipyrrin (21P-Ts). Following a general procedure,[12] $TiCl_4$ (1.22 mL, 11.1 mmol) was slowly added with stirring to dry THF (30 mL) under argon at 0 °C. The resulting yellow solution was slowly treated with $LiAlH_4$ (280 mg, 7.39 mmol). The resulting black mixture was stirred at room temperature for 15 min. TEA (9.66 mL, 69.3 mmol) was added. The resulting black mixture was stirred for 2 min at room temperature. The black mixture was slowly poured into a solution of **29-Ts** (648 mg, 1.54 mmol) in dry THF (25 mL). The mixture was stirred for 30 min at room temperature, and then water (30 mL) was added. The mixture was extracted with CH_2Cl_2 and ethyl acetate. The organic extract was washed with water, dried (Na_2SO_4), and chromatographed [silica, CH_2Cl_2/ethyl acetate (4:1)] to give a colorless oil (525 mg, 84%): ^{1}H NMR δ 0.90 (s, 3H), 1.08 (s, 3H), 2.40 (s, 3H), 2.37–2.49 (m, 2H), 2.72 (ABX, ^3J=9.6 Hz, ^2J=16.0 Hz, 1H), 2.98 (ABX, ^3J=4.8 Hz, ^2J=16.0 Hz, 1H), 3.38 (s, 3H), 3.39 (s, 3H), 3.81–3.85 (m, 1H), 4.79 (s, 1H), 6.21–6.24 (m, 2H), 7.27 (d, J=8.4 Hz, 2H), 7.29–7.31 (m, 1H), 7.65 (d, J=8.4 Hz, 2H); ^{13}C NMR δ 21.8, 22.8, 27.3, 28.2, 41.8, 48.7, 54.8, 54.9, 78.3, 103.2, 111.9, 113.9, 122.6, 127.0, 130.2, 133.9, 136.7, 145.0, 174.2; FABMS obsd 405.1840, calcd 405.1848 [$(M+H)^+$, M=$C_{21}H_{28}N_2O_4S$]. Anal. Calcd for

$C_{21}H_{28}N_2O_4S$: C, 62.35; H, 6.98; N, 6.93. Found: C, 62.20; H, 7.00; N, 6.70.

4.3.33. 4,4-Dimethyl-5-nitro-6-(*N*-*p*-tosyl-2-pyrrolyl)-2-hexanone (22-Ts). Following a general procedure,[12] CsF (526 mg, 3.47 mmol, 3.00 mol equiv, freshly dried by heating to 100 °C under vacuum for 1 h and then cooled to room temperature under argon) was placed in a flask under argon. A mixture of **9-Ts** (340 mg, 1.16 mmol) and mesityl oxide (**10c**, 1.98 mL, 17.3 mmol, 15.0 mol equiv) in dry acetonitrile (12 mL) was cannulated into the flask containing CsF. The mixture was heated at 70 °C for 16 h, whereupon the reaction was deemed to be complete by TLC. The reaction mixture was filtered through a bed of silica. The filtrate was concentrated and chromatographed [alumina, hexanes/ethyl acetate (3:1)] to give a pale yellow oil, which upon cooling (~ -6 °C) gave a pale yellow solid (330 mg, 73%): mp 92–93 °C; ^{1}H NMR δ 1.14 (s, 3H), 1.25 (s, 3H), 2.14 (s, 3H), 2.42 (s, 3H), 2.43, 2.57 (AB, ^{2}J=17.4 Hz, 2H), 3.21 (ABX, ^{3}J=2.2 Hz, ^{2}J=16.0 Hz, 1H), 3.37 (ABX, ^{3}J=12.0 Hz, ^{2}J=16.0 Hz, 1H), 5.12 (ABX, ^{3}J=2.2 Hz, ^{3}J=12.0 Hz, 1H), 6.02–6.03 (m, 1H), 6.16–6.18 (m, 1H), 7.24–7.26 (m, 1H), 7.32 (d, J=8.4 Hz, 2H), 7.60 (d, J=8.4 Hz, 2H); ^{13}C NMR δ 21.9, 23.8, 24.3, 26.7, 32.0, 36.9, 50.9, 94.2, 112.2, 114.8, 123.9, 126.6, 129.4, 130.4, 136.4, 145.4, 206.4. Anal. Calcd for $C_{19}H_{24}N_2O_5S$: C, 58.15; H, 6.16; N, 7.14. Found: C, 58.21; H, 6.17; N, 7.10.

4.3.34. 2,3,4,5-Tetrahydro-1,3,3-trimethyl-*N*^{11}-*p*-tosyldipyrrin *N*^{10}-oxide (23-Ts). Following a general procedure,[12] a vigorously stirred solution of **22-Ts** (225 mg, 0.574 mmol) in acetic acid (3.0 mL) and ethanol (3.0 mL) at 0 °C was treated slowly with zinc dust (932 mg, 14.3 mmol) in small portions for 5 min. The reaction mixture was stirred at 0 °C for 15 min and then filtered through Celite. The filtrate was concentrated under high vacuum. The resulting oil was purified by column chromatography [silica, CH_2Cl_2/ethyl acetate (1:1)$\rightarrow$$CH_2Cl_2$/methanol (9:1)] to afford a pale yellow oil (**2-Ts**, 47 mg, 24%) and the title compound as a white solid (119 mg, 57%). Data for the title compound: mp 123–125 °C; ^{1}H NMR δ 0.98 (s, 3H), 1.10 (s, 3H), 2.05–2.06 (m, 3H), 2.39 (s, 3H), 2.39–2.41 (m, 2H), 3.15 (ABX, ^{3}J=10.4 Hz, ^{2}J=16.0 Hz, 1H), 3.49 (ABX, ^{3}J=3.4 Hz, ^{2}J=16.0 Hz, 1H), 4.08–4.12 (m, 1H), 6.08–6.09 (m, 1H), 6.20–6.22 (m, 1H), 7.29 (d, J=8.2 Hz, 2H), 7.31–7.32 (m, 1H), 7.69 (d, J=8.2 Hz, 2H); ^{13}C NMR δ 13.3, 21.8, 23.4, 25.0, 29.1, 36.8, 47.4, 79.6, 111.7, 114.2, 123.1, 127.1, 130.3, 131.1, 136.0, 143.2, 145.2. Anal. Calcd for $C_{19}H_{24}N_2O_3S$: C, 63.31; H, 6.71; N, 7.77. Found: C, 63.27; H, 6.71; N, 7.70.

4.3.35. 1-Formyl-2,3,4,5-tetrahydro-3,3-dimethyl-*N*^{11}-*p*-tosyldipyrrin *N*^{10}-oxide (24-Ts). Following a general procedure,[27] a solution of **23-Ts** (590 mg, 1.64 mmol) in 1,4-dioxane (20.0 mL) was treated with SeO_2 (272 mg, 2.46 mmol) under argon. The mixture was stirred for 2.5 h at room temperature. The reaction mixture was treated with saturated aqueous $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2. The organic extract was washed with water, dried (Na_2SO_4), and chromatographed [silica, CH_2Cl_2/ethyl acetate (9:1)] to give a light brown solid (448 mg, 73%): mp 140–142 °C; IR 2965, 1665, 1524, 1368 cm^{-1}; ^{1}H NMR δ 1.06 (s, 3H), 1.10 (s, 3H), 2.41 (s, 3H), 2.57–2.59 (m, 2H), 3.06 (ABX, ^{3}J=9.2 Hz, ^{2}J=16.0 Hz, 1H), 3.43 (ABX, ^{3}J=4.4 Hz, ^{2}J=16.0 Hz, 1H), 4.38–4.43 (m, 1H), 6.13–6.15 (m, 1H), 6.23–6.25 (m, 1H), 7.31 (d, J=8.4 Hz, 2H), 7.32–7.34 (m, 1H), 7.68 (d, J=8.4 Hz, 2H), 10.13 (s, 1H); ^{13}C NMR δ 21.8, 22.6, 24.9, 27.5, 38.1, 39.8, 83.0, 112.0, 115.6, 123.7, 127.0, 129.8, 130.3, 136.0, 141.7, 145.4, 183.4. Anal. Calcd for $C_{19}H_{22}N_2O_4S$: C, 60.94; H, 5.92; N, 7.48. Found: C, 60.91; H, 5.85; N, 7.51.

4.3.36. 2,3,4,5-Tetrahydro-3,3-dimethyl-1-(1,3-dithian-2-yl)-*N*^{11}-*p*-tosyldipyrrin *N*^{10}-oxide (25-Ts). Following a general procedure,[41] a solution of **24-Ts** (100 mg, 0.27 mmol) and 1,3-propanedithiol (32 μL, 0.32 mmol) in CH_2Cl_2 (2.0 mL) was treated with neat $BF_3\cdot OEt_2$ (140 μL, 1.1 mmol) and powdered molecular sieves (4 Å, $\sim$200 mg). The mixture was stirred for 2 h at 0 °C, warmed to room temperature, and stirred for 40 h. Saturated aqueous $NaHCO_3$ ($\sim$2 mL) was added to the reaction mixture. The mixture was extracted with CH_2Cl_2. The organic extract was washed with water, dried (Na_2SO_4), and concentrated. The resulting residue was chromatographed [silica, CH_2Cl_2/ethyl acetate (4:1)] to give a pale yellow oil (52 mg, 42%): ^{1}H NMR δ 1.01 (s, 3H), 1.09 (s, 3H), 1.88–2.00 (m, 1H), 2.11–2.18 (m, 1H), 2.39 (s, 3H), 2.53–2.56 (m, 2H), 2.85–2.92 (m, 2H), 2.99–3.10 (m, 3H), 3.42–3.48 (m, 1H), 4.13–4.17 (m, 1H), 5.66 (s, 1H), 6.11–6.13 (m, 1H), 6.20–6.22 (m, 1H), 7.29 (d, J=8.4 Hz, 2H), 7.30–7.32 (m, 1H), 7.70 (d, J=8.4 Hz, 2H); ^{13}C NMR δ 21.8, 22.9, 24.8, 25.2, 28.2, 30.3, 37.7, 41.2, 43.0, 80.0, 111.8, 115.0. 123.2, 127.1, 130.3, 130.6, 135.9, 141.0, 145.3. The limited stability of this compound prevented high-resolution mass spectrometric analysis.

4.3.37. 2,3,4,5-Tetrahydro-3,3-dimethyl-1-(5,5-dimethyl-1,3-dioxan-2-yl)-*N*^{11}-*p*-tosyldipyrrin *N*^{10}-oxide (27-Ts). Following a general procedure,[43] a solution of **24-Ts** (224 mg, 0.600 mmol) and neopentyl glycol (81.0 mg, 0.78 mmol) in benzene (30.0 mL) was treated with *p*-toluenesulfonic acid monohydrate (11.4 mg, 0.060 mmol). The mixture was refluxed for 2.5 h and then cooled. The reaction mixture was washed with saturated aqueous $NaHCO_3$ and water. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed [silica, CH_2Cl_2/ethyl acetate (1:1)] to give a light brown solid (140 mg, 51%): mp 64–65 °C; ^{1}H NMR δ 0.75 (s, 3H), 1.00 (s, 3H), 1.09 (s, 3H), 1.21 (s, 3H), 2.39 (s, 3H), 2.54–2.56 (m, 2H), 3.10 (ABX, ^{3}J=10.0 Hz, ^{2}J=16.0 Hz, 1H), 3.45 (ABX, ^{3}J=3.6 Hz, ^{2}J=16.0 Hz, 1H), 3.56–3.61 (m, 2H), 3.63–3.69 (m, 2H), 4.15–4.19 (m, 1H), 5.66 (s, 1H), 6.10–6.12 (m, 1H), 6.19–6.22 (m, 1H), 7.28 (d, J=8.4 Hz, 2H), 7.30–7.32 (m, 1H), 7.69 (d, J=8.4 Hz, 2H); ^{13}C NMR δ 21.8, 22.1, 23.1, 24.7, 28.5, 29.9, 30.6, 37.5, 41.4, 77.5, 80.9, 94.3, 111.7, 114.7, 123.2, 127.1, 130.3, 130.8, 136.1, 141.6, 145.2; FABMS obsd 461.2100, calcd 461.2110 [$(M+H)^+$, M=$C_{24}H_{32}N_2O_5S$].

4.3.38. 1-(5,5-Dimethyl-1,3-dioxan-2-yl)-2,3,4,5-tetrahydro-3,3-dimethyl-*N*^{11}-*p*-tosyldipyrrin (28-Ts). Following a general procedure,[12] $TiCl_4$ (222 μL, 2.02 mmol) was slowly added with stirring to dry THF (5.0 mL) under argon at 0 °C. The resulting yellow solution was slowly treated with $LiAlH_4$ (51.0 mg, 1.35 mmol). The resulting black mixture was stirred at room temperature for 15 min. TEA (1.78 mL, 12.8 mmol) was added. The resulting black mixture was stirred for 2 min at room temperature. The black mixture was slowly poured into a solution of **27-Ts** (130 mg, 0.282 mmol) in dry THF (4.0 mL) at 0 °C. The mixture was stirred for 30 min at room temperature, and then water (8.0 mL) was added. The reaction mixture was extracted with CH_2Cl_2 and ethyl acetate. The organic extract was washed with water, dried (Na_2SO_4), and chromatographed [silica, CH_2Cl_2/ethyl acetate (19:1)] to give a colorless oil (116 mg, 92%): ^{1}H NMR δ 0.74 (s, 3H), 0.89 (s, 3H), 1.09 (s, 3H), 1.22 (s, 3H), 2.39 (s, 3H), 2.52–2.54 (m, 2H), 2.71 (ABX, $^3J=9.6$ Hz, $^2J=16.0$ Hz, 1H), 2.99 (ABX, $^3J=4.4$ Hz, $^2J=16.0$ Hz, 1H), 3.48–3.52 (m, 2H), 3.63–3.68 (m, 2H), 3.79–3.84 (m, 1H), 5.04 (s, 1H), 6.20–6.22 (m, 1H), 6.22–6.24 (m, 1H), 7.26 (d, $J=8.4$ Hz, 2H), 7.28–7.29 (m, 1H), 7.64 (d, $J=8.4$ Hz, 2H); ^{13}C NMR δ 21.8, 22.0, 22.7, 23.1, 27.1, 27.8, 30.5, 41.7, 48.6, 77.2, 78.3, 99.8, 111.8, 113.8, 122.4, 127.0, 130.1, 133.9, 136.6, 144.9, 173.8; FABMS obsd 445.2152, calcd 445.2161 [$(M+H)^+$, $M=C_{24}H_{32}N_2O_4S$].

4.3.39. 1-(Dimethoxymethyl)-2,3,4,5-tetrahydro-3,3-dimethyl-N^{11}-*p*-tosyldipyrrin N^{10}-oxide (29-Ts). Following a general procedure,[44] aldehyde **24-Ts** (287 mg, 0.766 mmol) was dissolved in a methanolic solution of $LaCl_3 \cdot 7H_2O$ (0.40 M, 1.9 mL). The resulting mixture was treated with trimethyl orthoformate (758 μL, 6.93 mmol) and stirred for 3 h at room temperature. The mixture was poured into 5% aqueous $NaHCO_3$ (16 mL). The mixture was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), concentrated, and chromatographed [silica, CH_2Cl_2/ethyl acetate (4:1)] to afford a white solid (180 mg, 56%): mp 108–109 °C; ^{1}H NMR δ 1.01 (s, 3H), 1.09 (s, 3H), 2.39 (s, 3H), 2.47–2.49 (m, 2H), 3.06–3.13 (m, 1H), 3.47 (s, 6H), 3.46–3.51 (m, 1H), 4.18–4.22 (m, 1H), 5.48 (s, 1H), 6.10–6.12 (m, 1H), 6.20–6.22 (m, 1H), 7.29 (d, $J=8.4$ Hz, 2H), 7.30–7.32 (m, 1H), 7.69 (d, $J=8.4$ Hz, 2H); ^{13}C NMR δ 21.8, 23.1, 24.8, 28.4, 37.7, 42.1, 55.4, 55.7, 80.7, 97.9, 111.8, 114.8. 123.3, 127.1, 130.3, 130.7, 136.0, 142.8, 145.3. Anal. Calcd for $C_{21}H_{28}N_2O_5S$: C, 59.98; H, 6.71; N, 6.66. Found: C, 59.82; H, 6.70; N, 6.50.

4.3.40. 1,1-Dimethoxy-4,4-dimethyl-5-nitro-6-(2-pyrrolyl)-2-hexanone (30). Following a general procedure,[12] CsF (8.97 g, 59.1 mmol, 3.00 mol equiv, freshly dried by heating to 100 °C under vacuum for 1 h and then cooled to room temperature under argon) was placed in a flask under argon. A mixture of **9** (2.76 g, 19.7 mmol) and acetal **10d** (13.7 g, 86.6 mmol, 4.40 mol equiv) in 170 mL of dry acetonitrile was cannulated into the flask containing CsF. The mixture was heated at 65 °C for 14 h, whereupon the reaction was deemed to be complete by TLC. The reaction mixture was filtered through a bed of alumina (ethyl acetate). The filtrate was concentrated and chromatographed [silica, hexanes/ethyl acetate (3:1)] to afford a brown oil containing some impurities. Chromatography (silica, CH_2Cl_2) gave a light brown solid (1.99 g, 34%): mp 74–75 °C; ^{1}H NMR δ 1.14 (s, 3H), 1.23 (s, 3H), 2.60, 2.72 (AB, $^2J=18.6$ Hz, 2H), 3.03 (ABX, $^3J=2.4$ Hz, $^2J=15.6$ Hz, 1H), 3.36 (ABX, $^3J=11.8$ Hz, $^2J=15.6$ Hz, 1H), 3.43 (s, 3H), 3.44 (s, 3H), 4.36 (s, 1H), 5.15 (ABX, $^3J=2.4$ Hz, $^3J=11.8$ Hz, 1H), 5.97–5.99 (m, 1H), 6.08–6.11 (m, 1H), 6.65–6.67 (m, 1H), 8.00–8.13 (br s, 1H); ^{13}C NMR δ 24.4, 24.5, 26.9, 36.6, 45.3, 55.4, 95.0, 104.9, 107.5, 108.9, 117.9, 126.2, 203.8; FABMS obsd 299.1605, calcd 299.1607. Anal. Calcd for $C_{14}H_{22}N_2O_5$: C, 56.36; H, 7.43; N, 9.39. Found: C, 56.44; H, 7.57; N, 9.38.

4.3.41. Solventless synthesis of 30. Following a reported procedure,[18] a sample of **9** (1.44 g, 10.0 mmol) was treated with **10d** (1.90 g, 12.0 mmol) and DBU (4.57 g, 30.0 mmol). The reaction mixture was stirred for 16 h and then diluted with CH_2Cl_2. The mixture was washed with water and brine. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed (silica, CH_2Cl_2) to give a light brown oil, which solidified to a pale-brown solid (1.75 g, 53%). The characterization data were identical as those described above.

4.3.42. 2,3,4,5-Tetrahydro-1-(dimethoxymethyl)-3,3-dimethyldipyrrin N^{10}-oxide (31). Following a general procedure,[12] a vigorously stirred solution of **30** (60 mg, 0.20 mmol) in acetic acid (1.0 mL) and ethanol (1.0 mL) at 0 °C was treated slowly with zinc dust (330 mg, 5.0 mmol) in small portions for 5 min. The reaction mixture was stirred at 0 °C for 15 min and filtered through Celite. The filtrate was concentrated under high vacuum. The resulting oil was chromatographed [alumina, CH_2Cl_2/ethyl acetate (9:1)] to afford a white solid (9.0 mg, 17%): mp 68–70 °C; ^{1}H NMR δ 1.11 (s, 3H), 1.21 (s, 3H), 2.47, 2.53 (AB, $^2J=17.8$ Hz, 2H), 2.96 (ABX, $^3J=1.6$ Hz, $^2J=15.8$ Hz, 1H), 3.07 (ABX, $^3J=7.6$ Hz, $^2J=15.8$ Hz, 1H), 3.43 (s, 3H), 3.46 (s, 3H), 3.95 (ABX, $^3J=1.6$ Hz, $^2J=7.6$ Hz, 1H), 5.48 (s, 1H), 5.92–5.95 (m, 1H), 6.06–6.09 (m, 1H), 6.68–6.71 (m, 1H), 10.31–10.45 (br s, 1H); ^{13}C NMR δ 22.8, 25.5, 27.3, 38.4, 42.2, 55.3, 55.5, 82.9, 97.6, 106.4, 107.5, 117.8, 128.9, 145.1; FABMS obsd 266.1630, calcd 266.1630 ($M=C_{14}H_{22}N_2O_3$).

4.3.43. 2,3-Dihydro-1-(dimethoxymethyl)-3,3-dimethyldipyrrin (32P). Following a general procedure,[10] a solution of acetal **30** (149 mg, 0.500 mmol) in dry THF (5.0 mL) was treated with sodium methoxide (135 mg, 2.50 mmol). The resulting mixture was stirred at room temperature under argon for 1 h to form the nitronate anion. $TiCl_3$ (8.6 wt % $TiCl_3$ in 28 wt % HCl, 3.74 mL, 2.50 mmol, 5 mol equiv) was placed in a flask to which 20 mL of water was added. Ammonium acetate (15.4 g, 200 mmol, 400 mol equiv) was added to buffer the solution to pH ~6 (pH meter), and then 1.2 mL of THF was added. The nitronate anion in THF was added to the buffered $TiCl_3$ solution. The resulting mixture was stirred at room temperature for 4.5 h. The reaction mixture was extracted with ethyl acetate. The organic layer was washed [aqueous $NaHCO_3$ (10% w/v, 40 mL) and water], dried, and concentrated under reduced pressure. The resulting oil was purified by column chromatography [alumina, packed in hexanes and eluted with hexanes/ethyl acetate (2:1)] to give a yellow oil (17 mg, 14%): ^{1}H NMR δ 1.21 (s, 6H), 2.61 (s, 2H), 3.45 (s, 6H), 5.02 (s, 1H), 5.88 (s, 1H), 6.15–6.18 (m, 1H), 6.83–6.86 (m, 1H), 10.59–10.70 (br s, 1H); ^{13}C NMR δ 29.3, 40.2, 48.3, 54.8, 103.0, 107.7, 108.7, 109.4, 119.6, 130.9, 159.5, 174.1; λ_{abs} (CH_2Cl_2) 341 nm. The limited stability of this compound thwarted high-resolution mass spectrometric analysis.

4.3.44. 2,3,4,5-Tetrahydro-1-(α-hydroxy-α-phenylmethyl)-3,3-dimethyl-N^{11}-*p*-tosyldipyrrin N^{10}-oxide (33-Ts). A solution of **24-Ts** (573 mg, 1.53 mmol) in dry

THF (23.0 mL) at 0 °C was treated with PhMgBr (1.84 mL, 1.0 M in THF, 1.84 mmol). The mixture was stirred for 1.5 h at 0 °C. The reaction was quenched by the addition of H_2O/hexanes (20 mL). The reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine. TLC analysis (silica, ethyl acetate) showed two components with R_f=0.65 (**33a**-**Ts**) and R_f=0.49 (**33b**-**Ts**). Column chromatography (silica, ethyl acetate) afforded the two isomers as a light brown solid (**33a-Ts**, 113 mg, 16%) and a white solid (**33b-Ts**, 126 mg, 18%). Data for **33a**-**Ts**: mp 62–64 °C; ^{1}H NMR δ 0.89 (s, 3H), 1.01 (s, 3H), 2.18, 2.32 (AB, ^{2}J=17.6 Hz, 2H), 2.40 (s, 3H), 3.07 (ABX, ^{3}J=9.8 Hz, ^{2}J=15.8 Hz, 1H), 3.47 (ABX, ^{3}J=4.2 Hz, ^{2}J=15.8 Hz, 1H), 4.21–4.25 (m, 1H), 5.62 (s, 1H), 6.07–6.09 (m, 1H), 6.18–6.20 (m, 1H), 6.86–6.97 (br s, 1H), 7.29 (d, J=8.2 Hz, 2H), 7.29–7.31 (m, 1H), 7.32–7.35 (m, 1H), 7.36–7.42 (m, 2H), 7.42–7.46 (m, 2H), 7.68 (d, J=8.2 Hz, 2H); ^{13}C NMR δ 21.8, 22.7, 24.7, 28.1, 37.9, 44.0, 70.9, 80.3, 111.9, 114.9, 123.3, 126.5, 127.0, 128.5, 128.9, 130.3, 130.4, 135.9, 139.5, 145.3, 148.2; FABMS obsd 453.1854, calcd 453.1848 ($C_{25}H_{28}N_2O_4S$). Data for **33b**-**Ts**: mp 156–158 °C; ^{1}H NMR δ 0.96 (s, 3H), 0.97 (s, 3H), 2.23–2.26 (m, 2H), 2.40 (s, 3H), 3.15 (ABX, ^{3}J=9.8 Hz, ^{2}J=16.0 Hz, 1H), 3.48 (ABX, ^{3}J=4.0 Hz, ^{2}J=16.0 Hz, 1H), 4.13–4.19 (m, 1H), 5.60–5.62 (m, 1H), 6.09–6.11 (m, 1H), 6.20–6.22 (m, 1H), 7.01–7.03 (m, 1H), 7.30 (d, J=8.6 Hz, 2H), 7.30–7.33 (m, 1H), 7.32–7.35 (m, 1H), 7.36–7.41 (m, 2H), 7.42–7.46 (m, 2H), 7.68 (d, J=8.6 Hz, 2H); ^{13}C NMR δ 21.8, 22.9, 24.8, 28.3, 37.9, 44.2, 71.4, 80.7, 111.9, 114.8, 123.3, 126.6, 127.0, 128.6, 129.0, 130.3, 130.5, 136.0, 139.5, 145.4, 148.0; FABMS obsd 453.1859, calcd 453.1848 ($C_{25}H_{28}N_2O_4S$).

4.3.45. 9-Bromo-2,3,4,5-tetrahydro-1,3,3-trimethyldipyrrin N^{10}-oxide (34). Following a general procedure,[10] a solution of **23** (413 mg, 2.00 mmol) in dry THF (20.0 mL) was cooled to −78 °C under argon. NBS (356 mg, 2.00 mmol) was added in two portions. The reaction mixture was stirred for 1 h at −78 °C. Hexanes (25 mL) and water (25 mL) were added. The mixture was allowed to warm to room temperature. The mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), concentrated under vacuum without heat, and chromatographed (silica, ethyl acetate) to give a white solid (453 mg, 79%): mp 124–125 °C (dec); ^{1}H NMR δ 1.09 (s, 3H), 1.19 (s, 3H), 2.07–2.08 (m, 3H), 2.32, 2.48 (AB, ^{2}J=17.6 Hz, 2H), 2.91 (ABX, ^{3}J=2.8 Hz, ^{2}J=15.6 Hz, 1H), 3.00 (ABX, ^{3}J=7.2 Hz, ^{2}J=15.6 Hz, 1H), 3.84–3.91 (m, 1H), 5.85–5.87 (m, 1H), 5.96–5.98 (m, 1H), 10.92–11.03 (br s, 1H); ^{13}C NMR δ 13.4, 23.0, 26.2, 27.8, 37.4, 47.2, 81.1, 96.8, 108.1, 109.4, 130.5, 146.3. Anal. Calcd for $C_{12}H_{17}BrN_2O$: C, 50.54; H, 6.01; N, 9.82. Found: C, 50.48; H, 6.05; N, 9.65.

4.3.46. 9-Bromo-1-formyl-2,3,4,5-tetrahydro-3,3-dimethyldipyrrin N^{10}-oxide (35). Following a general procedure,[27] a solution of **34** (29 mg, 0.10 mmol) in 1,4-dioxane (1.0 mL) was treated with SeO_2 (14 mg, 0.13 mmol) under argon. The mixture was stirred for 2.5 h at room temperature. The reaction mixture was then treated with saturated aqueous $NaHCO_3$ (1.0 mL) and extracted with ethyl acetate. The organic extract was washed with water, dried (Na_2SO_4), and chromatographed [silica, hexanes/ethyl acetate (1:1)] to give a light brown solid (13 mg, 43%): mp 115–117 °C (dec); ^{1}H NMR δ 1.09 (s, 3H), 1.27 (s, 3H), 2.60 (AB, ^{2}J=17.2 Hz, 1H), 2.66 (AB, ^{2}J=17.2 Hz, 1H), 2.84 (ABX, ^{3}J=2.2 Hz, ^{2}J=16.0 Hz, 1H), 3.08 (ABX, ^{3}J=8.2 Hz, ^{2}J=16.0 Hz, 1H), 4.06–4.11 (m, 1H), 5.88–5.90 (m, 1H), 5.99–6.01 (m, 1H), 9.64–9.74 (br s, 1H), 10.20 (s, 1H); ^{13}C NMR δ 22.2, 25.2, 26.4, 38.9, 39.9, 85.4, 97.4, 108.7, 110.0, 129.8, 142.7, 183.1; FABMS obsd 299.0385, calcd 299.0395 [$(M+H)^+$, M=$C_{12}H_{15}BrN_2O_2$].

4.3.47. 6-(5-Formylpyrrol-2-yl)-1,1-dimethoxy-4,4-dimethyl-5-nitrohexan-2-one (36). A solution of **30** (0.289 g, 1.00 mmol) in CH_2Cl_2 (2 mL) and DMF (1 mL) was treated dropwise at 0 °C with $POCl_3$ (0.100 mL, 1.09 mmol). The resulting mixture was stirred at 0 °C for 1 h, and then poured into ice-cooled 10% aqueous NaOH (20 mL). The resulting mixture was stirred for 30 min, and then extracted with CH_2Cl_2. The organic extract was washed (water and brine), dried (Na_2SO_4), and concentrated. Chromatography (silica, CH_2Cl_2) afforded a yellow oil, which solidified to a yellow solid (0.111 g, 35%): mp 103–104 °C; ^{1}H NMR δ 1.16 (s, 3H), 1.26 (s, 3H), 2.64 (AB, ^{2}J=18.4 Hz, 1H), 2.72 (AB, ^{2}J=18.4 Hz, 1H), 3.16 (ABX, ^{3}J=2.4 Hz, ^{2}J=15.2 Hz, 1H), 3.42 (s, 3H), 3.43 (s, 3H), 3.45 (m, overlapped, 1H), 4.35 (s, 1H), 5.23 (ABX, ^{3}J=2.4 Hz, ^{2}J=11.6 Hz, 1H), 6.10–6.11 (m, 1H), 6.86–6.88 (m, 1H), 6.38 (s, 1H), 10.42–10.46 (br s, 1H); ^{13}C NMR δ 24.2, 24.3, 27.1, 36.8, 45.0, 52.47, 52.51, 94.0, 105.0, 111.0, 122.9, 133.0, 136.8, 179.1, 203.6; FABMS obsd 327.1569, calcd 327.1556 [$(M+H)^+$, M=$C_{15}H_{22}N_2O_6$].

4.3.48. 9-Formyl-2,3-dihydro-1-(dimethoxymethyl)-3,3-dimethyldipyrrin (37). Following a general procedure,[18] a sample of **36** (32.6 mg, 0.100 mmol) in THF/H_2O (1 mL, 1:1) was treated with NH_4Cl (16.0 mg, 0.300 mmol) and zinc dust (98.0 mg, 1.50 mmol). The resulting mixture was stirred at room temperature for 1 h. Ethyl acetate (10 mL) was added, and the resulting mixture was filtered. The filtrate was washed (water and brine), dried (Na_2SO_4), and concentrated. Chromatography [silica, CH_2Cl_2/ethyl acetate (1:2)] afforded a white solid (12.5 mg, 45%): mp 69–71 °C; ^{1}H NMR δ 1.09, (s, 3H), 1.20 (s, 3H), 2.44–2.56 (m, 2H), 2.98 (ABX, ^{3}J=3.2 Hz, ^{2}J=16.0 Hz, 1H), 3.14 (ABX, ^{3}J=7.8 Hz, ^{2}J=16.0 Hz, 1H), 3.46 (s, 3H), 3.49 (s, 3H), 3.98–4.00 (m, 1H), 5.50 (s, 1H), 6.07–6.08 (m, 1H), 6.81–6.82 (m, 1H), 9.42 (s, 1H), 11.36–11.44 (br s, 1H); ^{13}C NMR δ 22.9, 25.7, 27.3, 29.9, 38.4, 41.9, 55.8, 56.1, 81.7, 110.4, 121.0, 133.2, 138.0, 145.5, 178.6; FABMS obsd 279.1696, calcd 279.1709 [$(M+H)^+$, M=$C_{15}H_{22}N_2O_3$].

4.3.49. 9-Bromo-2,3,4,5-tetrahydro-1,3,3-trimethyldipyrrin (38). Following a procedure for the α-bromination of pyrroles,[10] a solution of **2** (95 mg, 0.50 mmol) in dry THF (10 mL) was cooled to −78 °C under argon. NBS (89 mg, 0.50 mmol) was added in two portions. The reaction mixture was stirred for an additional 1 h at −78 °C. Hexanes (6.0 mL) and water (6.0 mL) were added, and the mixture was allowed to warm to room temperature. The organic layer was extracted with ethyl acetate, dried ($MgSO_4$), and concentrated under vacuum without heating. The resulting residue was purified by gravity column chromatography (silica, ethyl acetate) to give a white solid (112 mg, 83%): mp

102–104 °C (dec); ^{1}H NMR δ 0.92 (s, 3H), 1.11 (s, 3H), 2.04–2.06 (m, 3H), 2.26–2.41 (m, 2H), 2.49–2.57 (m, 1H), 2.69–2.71 (m, 1H), 3.55–3.62 (m, 1H), 5.85–5.87 (m, 1H), 5.98–6.00 (m, 1H), 9.84–10.00 (br s, 1H); ^{13}C NMR δ 20.7, 23.0, 27.4, 28.3, 42.0, 54.5, 80.2, 95.7, 107.2, 109.4, 133.4, 175.0; FABMS obsd 269.0641, calcd 269.0653 [(M+H)$^+$, M=$C_{12}H_{17}BrN_2$].

4.3.50. 9-Formyl-2,3,4,5-tetrahydro-1,3,3-trimethyldipyrrin (39) by reductive cyclization. Following a general procedure,[18] a solution of **40** (0.226 g, 1.00 mmol) in THF was treated with $HCOONH_4$ (0.996 g, 15.8 mmol) and zinc dust (0.981 g, 15.0 mmol). The resulting suspension was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate and filtered. The filter cake was washed with ethyl acetate (∼20 mL). The filtrate was washed (water and brine), dried (Na_2SO_4), and concentrated. The crude product (dark red) was chromatographed [silica, ethyl acetate/methanol (10:1)] to afford a dark orange solid (60 mg, 27%): mp 72–74 °C; ^{1}H NMR δ 0.93 (s, 3H), 1.12 (s, 3H), 2.04 (s, 3H), 2.30 (AB, ^2J=17.0 Hz, 1H), 2.39 (AB, ^2J=17.0 Hz, 1H), 2.62 (ABX, ^3J=11.2 Hz, ^2J=15.2 Hz, 1H), 2.79 (ABX, ^3J=3.2 Hz, ^2J=15.2 Hz, 1H), 3.62–3.65 (m, 1H), 6.09–6.10 (m, 1H), 6.85–6.86 (m, 1H), 9.39 (s, 1H), 10.72–10.95 (br s, 1H); ^{13}C NMR δ 20.7, 23.1, 27.3, 28.3, 42.2, 54.6, 79.2, 109.9, 121.9, 132.5, 141.7, 175.3, 178.4; FABMS obsd 219.1491, calcd 219.1497 [(M+H)$^+$, M=$C_{13}H_{18}N_2O$].

4.3.51. Synthesis of 39 by Vilsmeier formylation. A solution of **2** (0.380 g, 2.00 mmol) in DMF (0.70 mL) and CH_2Cl_2 (16.0 mL) at 0 °C under argon was treated dropwise with $POCl_3$ (0.229 mL, 2.50 mmol). The reaction mixture was stirred at 0 °C for 1 h and then brought to room temperature. The reaction mixture was poured into 2.5 M NaOH (10 mL) at 0 °C. Water was added (250 mL), and the resulting mixture was extracted with CH_2Cl_2. The organic layer was washed (water and brine), dried (Na_2SO_4), and concentrated. The crude product (red-brown) was chromatographed [silica, ethyl acetate/methanol (10:1)] to afford a yellow solid (0.24 g, 55%). A brownish yellow oil byproduct also was obtained and identified as 1,11-diformyl-2,3-dihydro-1,3,3-trimethyldipyrromethane (**42**, 0.17 g, 35%). The data for the title compound (mp, ^{1}H NMR, ^{13}C NMR, and FABMS) were consistent with those obtained from samples prepared via an earlier route. Data for **42**: ^{1}H NMR δ 1.01 (s, 3H), 1.02 (s, 3H), 1.93 (s, 3H), 3.0 (ABX, ^3J=8.8 Hz, ^2J=15.6 Hz, 1H), 3.15 (ABX, ^3J=4.4 Hz, ^2J=15.6 Hz, 1H), 4.34–4.37 (m, 1H), 4.77 (s, 1H), 6.11–6.12 (m, 1H), 6.86–6.87 (m, 1H), 8.38 (s, 1H), 9.35 (s, 1H), 10.52–10.65 (br s, 1H); ^{13}C NMR δ 12.8, 22.4, 28.1, 30.6, 43.8, 66.0, 110.6, 120.9, 122.7, 132.3, 133.8, 140.0, 157.8, 178.5; FABMS obsd 247.1439, calcd 247.1447 [(M+H)$^+$, M=$C_{14}H_{18}N_2O_2$].

4.3.52. 6-(5-Formyl-2-pyrrolyl)-4,4-dimethyl-5-nitrohexan-2-one (40). A solution of **22** (2.74 g, 11.5 mmol) in DMF (3.7 mL) and CH_2Cl_2 (85 mL) at 0 °C under argon was treated dropwise with $POCl_3$ (1.25 mL, 13.6 mmol). The reaction mixture changed from light brown to dark red. The residue was stirred at 0 °C for 1 h and then brought to room temperature and stirred overnight. The reaction mixture was poured into 2.5 M aqueous NaOH (60 mL) at 0 °C. Water (250 mL) was added, and the reaction mixture was extracted with CH_2Cl_2. The organic extract was washed (water and brine), dried (Na_2SO_4), and concentrated. Chromatography [silica, hexanes/ethyl acetate (1:1)] afforded a yellow solid (1.97 g, 64%). A light pink byproduct also was isolated (0.090 g, 32%) and identified as 2,3,4-trihydro-4,4,6-trimethyl-3-nitrocycloheptene[*b*]pyrrole (**40′**). Data for **40**: mp 105–107 °C; ^{1}H NMR δ 1.13 (s, 3H), 1.28 (s, 3H), 2.15 (s, 3H), 2.43 (AB, ^2J=18.0 Hz, 1H), 2.62 (AB, ^2J=18.0 Hz, 1H), 3.14 (ABX, ^3J=2.4 Hz, ^2J=15.4 Hz, 1H), 3.58 (ABX, ^3J=12.0 Hz, ^2J=15.4 Hz, 1H), 5.24 (ABX, ^3J=2.4 Hz, ^3J=12.0 Hz, 1H), 6.11–6.14 (m, 1H), 6.87–6.88 (m, 1H), 9.39 (s, 1H), 10.20–10.32 (br s, 1H); ^{13}C NMR δ 24.1, 24.6, 27.0, 32.0, 37.1, 51.5, 93.7, 111.1, 123.1, 132.9, 136.8, 179.1, 206.9; FABMS obsd 267.1353, calcd 267.1345 [(M+H)$^+$, M=$C_{13}H_{18}N_2O_4$]. Data for **40′**: mp 182–185 °C; ^{1}H NMR δ 1.20 (s, 3H), 1.23 (s, 3H), 2.06 (s, 3H), 3.42 (ABX, ^3J=3.8 Hz, ^2J=18.0 Hz, 1H), 3.74 (ABX, ^3J=3.8 Hz, ^2J=17.2 Hz, 1H), 4.78 (ABX, ^3J=3.6 Hz, ^3J=10.8 Hz, 1H), 5.36 (s, 1H), 6.92–6.93 (s, 1H), 9.42 (s, 1H), 10.12–10.23 (br s, 1H); ^{13}C NMR δ 23.0, 24.2, 29.0, 29.5, 29.8, 39.0, 89.4, 121.6, 123.6, 127.6, 131.4, 134.3, 179.3; FABMS obsd 249.1226, calcd 249.1239 [(M+H)$^+$, M=$C_{13}H_{16}N_2O_3$].

4.3.53. 2,3,4,5-Tetrahydro-1,3,3,9-tetramethyldipyrrin *N*-oxide (41). Following a general procedure,[12] a vigorously stirred solution of **40** (0.26 g, 1.0 mmol) in acetic acid (5.0 mL) and ethanol (5.0 mL) was treated slowly with zinc dust (1.64 g, 25.0 mmol) in small portions over 5 min at 0 °C. The starting material was consumed in 2 h at 0 °C. The reaction mixture was filtered. The filter cake was washed with ethyl acetate (∼20 mL). The filtrate was neutralized with aqueous $NaHCO_3$, washed (water and brine), dried (Na_2SO_4), and concentrated. The resulting red oil was chromatographed [silica, hexanes/ethyl acetate/methanol (8:5:2)] to afford a light brown solid (39.0 mg, 18%): mp 98–100 °C; ^{1}H NMR δ 1.11 (s, 3H), 1.18 (s, 3H), 2.04–2.05 (m, 3H), 2.22 (s, 3H), 2.29 (AB, ^2J=17.6 Hz, 1H), 2.43 (AB, ^2J=17.6 Hz, 1H), 2.91–3.01 (m, 2H), 3.84–3.86 (m, 1H), 5.66–5.71 (m, 1H), 5.77–5.79 (m, 1H), 10.10–10.24 (br s, 1H); ^{13}C NMR δ 13.38, 13.41, 23.0, 26.1, 26.6, 28.0, 37.3, 47.2, 81.6, 105.0, 106.3, 127.6, 145.7; FABMS obsd 220.1562, calcd 220.1567 ($C_{13}H_{20}N_2O$).

Acknowledgements

This work was funded by the NIH (GM36238). We thank Dr. Man Nyoung Kim for the synthesis of **38** and exploratory studies on reactions of **9**.

References and notes

1. (a) Vernon, L. P.; Seely, G. R. *The Chlorophylls*; Academic: New York, NY, USA, 1966; (b) *Chlorophylls*; Scheer, H., Ed.; CRC: Boca Raton, FL, USA, 1991.
2. (a) Agius, L.; Ballantine, J. A.; Ferrito, V.; Jaccarini, V.; Murray-Rust, P.; Pelter, A.; Psaila, A. F.; Schembri, P. J. *Pure Appl. Chem.* **1979**, *51*, 1847–1864; (b) Helaja, J.; Montforts, F.-P.; Kilpeläinen, I.; Hynninen, P. H. *J. Org. Chem.* **1999**, *64*, 432–437.

3. (a) Prinsep, M. R.; Caplan, F. R.; Moore, R. E.; Patterson, G. M. L.; Smith, C. D. *J. Am. Chem. Soc.* **1992**, *114*, 385–387; (b) Prinsep, M. R.; Patterson, G. M. L.; Larsen, L. K.; Smith, C. D. *Tetrahedron* **1995**, *51*, 10523–10530.
4. (a) Crane, B. R.; Getzoff, E. D. *Curr. Opin. Struct. Biol.* **1996**, *6*, 744–756; (b) Nakayama, M.; Akashi, T.; Hase, T. *J. Inorg. Biochem.* **2000**, *82*, 27–32.
5. (a) *Chemistry*; Dolphin, D., Ed.; B_{12}; Wiley-Interscience: New York, NY, USA, 1982; Vol. 1; (b) *Biochemistry and Medicine*; Dolphin, D., Ed.; B_{12}; Wiley-Interscience: New York, NY, USA, 1982; Vol. 2; (c) *Vitamin B_{12} and B_{12}-Proteins*; Kräutler, B., Arigoni, D., Golding, B. T., Eds.; Wiley-VCH: Weinheim, 1998.
6. Ragsdale, S. W. *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic: San Diego, CA, 2003; Vol. 11, pp 205–228.
7. (a) Dorough, G. D.; Miller, J. R. *J. Am. Chem. Soc.* **1952**, *74*, 6106–6108; (b) Dorough, G. D.; Huennekens, F. M. *J. Am. Chem. Soc.* **1952**, *74*, 3974–3976; (c) Whitlock, H. W., Jr.; Hanauer, R.; Oester, M. Y.; Bower, B. K. *J. Am. Chem. Soc.* **1969**, *91*, 7485–7489.
8. (a) Eschenmoser, A.; Wintner, C. E. *Science* **1977**, *196*, 1410–1420; (b) Flitsch, W. *Adv. Heterocycl. Chem.* **1988**, *43*, 73–126; (c) Woodward, R. B.; Ayer, W. A.; Beaton, J. M.; Bickelhaupt, F.; Bonnett, R.; Buchschacher, P.; Closs, G. L.; Dutler, H.; Hannah, J.; Hauck, F. P.; Ito, S.; Langemann, A.; Le Goff, E.; Leimgruber, W.; Lwowski, W.; Sauer, J.; Valenta, Z.; Volz, H. *Tetrahedron* **1990**, *46*, 7599–7659; (d) Montforts, F.-P.; Gerlach, B.; Höper, F. *Chem. Rev.* **1994**, *94*, 327–347; (e) Montforts, F.-P.; Glasenapp-Breiling, M. *Prog. Heterocycl. Chem.* **1998**, *10*, 1–24; (f) Montforts, F.-P.; Glasenapp-Breiling, M. *Fortschr. Chem. Org. Naturst.* **2002**, *84*, 1–51; (g) Riether, D.; Mulzer, J. *Eur. J. Org. Chem.* **2003**, 30–45.
9. Balaban, T. S.; Tamiaki, H.; Holzwarth, A. R. *Top. Curr. Chem.* **2005**, *258*, 1–38.
10. Strachan, J.-P.; O'Shea, D. F.; Balasubramanian, T.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 3160–3172.
11. Balasubramanian, T.; Strachan, J. P.; Boyle, P. D.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 7919–7929.
12. Taniguchi, M.; Ra, D.; Mo, G.; Balasubramanian, T.; Lindsey, J. S. *J. Org. Chem.* **2001**, *66*, 7342–7354.
13. Taniguchi, M.; Kim, H.-J.; Ra, D.; Schwartz, J. K.; Kirmaier, C.; Hindin, E.; Diers, J. R.; Prathapan, S.; Bocian, D. F.; Holten, D.; Lindsey, J. S. *J. Org. Chem.* **2002**, *67*, 7329–7342.
14. Laha, J. K.; Muthiah, C.; Taniguchi, M.; McDowell, B. E.; Ptaszek, M.; Lindsey, J. S. *J. Org. Chem.* **2006**, *71*, 4092–4102.
15. Kim, H.-J.; Lindsey, J. S. *J. Org. Chem.* **2005**, *70*, 5475–5486.
16. Dutton, C. J.; Fookes, C. J. R.; Battersby, A. R. *J. Chem. Soc., Chem. Commun.* **1983**, 1237–1238.
17. Battersby, A. R.; Dutton, C. J.; Fookes, C. J. R. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1569–1576.
18. Ptaszek, M.; Bhaumik, J.; Kim, H.-J.; Taniguchi, M.; Lindsey, J. S. *Org. Process Res. Dev.* **2005**, *9*, 651–659.
19. Inhoffen, H. H.; Petrovicki, W.; Gossauer, A. *Liebigs Ann. Chem.* **1973**, 1067–1074.
20. Harrison, P. J.; Fookes, C. J. R.; Battersby, A. R. *J. Chem. Soc., Chem. Commun.* **1981**, 797–799.
21. Arnott, D. M.; Battersby, A. R.; Harrison, P. J.; Henderson, G. B.; Sheng, Z.-C. *J. Chem. Soc., Chem. Commun.* **1984**, 525–526.
22. Battersby, A. R.; Reiter, L. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2743–2749.
23. Harrison, P. J.; Sheng, Z.-C.; Fookes, C. J. R.; Battersby, A. R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1667–1678.
24. Arnott, D. M.; Harrison, P. J.; Henderson, G. B.; Sheng, Z.-C.; Leeper, F. J.; Battersby, A. R. *J. Chem. Soc., Perkin Trans. 1* **1989**, 265–278.
25. Battersby, A. R.; Block, M. H.; Fookes, C. J. R.; Harrison, P. J.; Henderson, G. B.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2175–2187.
26. Battersby, A. R.; Block, M. H.; Leeper, F. J.; Zimmerman, S. C. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2189–2195.
27. Jacobi, P. A.; Lanz, S.; Ghosh, I.; Leung, S. H.; Löwer, F.; Pippin, D. *Org. Lett.* **2001**, *3*, 831–834.
28. O'Neal, W. G.; Roberts, W. P.; Ghosh, I.; Jacobi, P. A. *J. Org. Chem.* **2005**, *70*, 7243–7251.
29. O'Neal, W. G.; Roberts, W. P.; Ghosh, I.; Wang, H.; Jacobi, P. A. *J. Org. Chem.* **2006**, *71*, 3472–3480.
30. Battersby, A. R.; Fookes, C. J. R.; Snow, R. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2725–2732.
31. Tietze, L. F.; Kettschau, G.; Heitmann, K. *Synthesis* **1996**, 851–857.
32. Cheruku, S. R.; Padmanilayam, M. P.; Vennerstrom, J. L. *Tetrahedron Lett.* **2003**, *44*, 3701–3703.
33. Park, K.-H.; Marshall, W. J. *J. Org. Chem.* **2005**, *70*, 2075–2081.
34. Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061–5087.
35. Anderson, H. J.; Loader, C. E.; Xu, R. X.; Le, N.; Gogan, N. J.; McDonald, R.; Edwards, L. G. *Can. J. Chem.* **1985**, *63*, 896–902.
36. Settambolo, R.; Lazzaroni, R.; Messeri, T.; Mazzetti, M.; Salvadori, P. *J. Org. Chem.* **1993**, *58*, 7899–7902.
37. Abell, A. D.; Nabbs, B. K.; Battersby, A. R. *J. Org. Chem.* **1998**, *63*, 8163–8169.
38. Hasegawa, M.; Taniyama, D.; Tomioka, K. *Tetrahedron* **2000**, *56*, 10153–10158.
39. (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149–164; (b) Gerspacher, M.; Rapoport, H. *J. Org. Chem.* **1991**, *56*, 3700–3706; (c) Reed, P. E.; Katzenellenbogen, J. A. *J. Org. Chem.* **1991**, *56*, 2624–2634; (d) Lubell, W. D.; Jamison, T. F.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3511–3522; (e) Myers, A. G.; Kung, D. W.; Zhong, B.; Movassaghi, M.; Kwon, S. *J. Am. Chem. Soc.* **1999**, *121*, 8401–8402; (f) Lubell, W. D.; Rapport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236–239; (g) Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Gawronski, J.; Mazzanti, G.; Ricci, A.; Varchi, G. *Eur. J. Org. Chem.* **1999**, 437–445.
40. Black, D. St. C.; Strauch, R. J. *Aust. J. Chem.* **1988**, *41*, 183–193.
41. Patrocínio, A. F.; Moran, P. J. S. *J. Organomet. Chem.* **2000**, *603*, 220–224.
42. Lindsey, J. S.; Brown, P. A.; Siesel, D. A. *Tetrahedron* **1989**, *45*, 4845–4866.
43. Nagata, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3005–3016.
44. Luche, J.-L.; Gemal, A. L. *J. Chem. Soc., Chem. Commun.* **1978**, 976–977.
45. Kantam, M. L.; Swapna, V.; Santhi, P. L. *Synth. Commun.* **1995**, *25*, 2529–2532.
46. Lindsey, J. S.; Prathapan, S.; Johnson, T. E.; Wagner, R. W. *Tetrahedron* **1994**, *50*, 8941–8968.
47. Kim, H.-J. Ph.D. thesis, North Carolina State University, 2005.
48. (a) Lee, C.-H.; Li, F.; Iwamoto, K.; Dadok, J.; Bothner-By, A. A.; Lindsey, J. S. *Tetrahedron* **1995**, *51*, 11645–11672; (b) Rao, P. D.; Dhanalekshmi, S.; Littler, B. J.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 7323–7344.
49. Battersby, A. R.; Dutton, C. J.; Fookes, C. J. R.; Turner, S. P. D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1557–1567.
50. Ghosh, I.; Jacobi, P. A. *J. Org. Chem.* **2002**, *67*, 9304–9309.