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Synthesis of Hydrodipyrins Tailored for Reactivity at the 1- and 9-Positions

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Abstract

A collection of 33 hydrodipyrins (9 targets, 21 intermediates, and 3 byproducts) has been prepared. The hydrodipyrins (dihydrodipyrins, tetrahydrodipyrins, and hexahydrodipyrins) 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, CH₃, 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 hydrodipyrins should facilitate development of syntheses of diverse hydroporphyrins.

Keywords

Hydrodipyrin; 1-Pyrroline; Pyrrole; Hydroporphyrin

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. Chlorophyll *a* and *b* (chlorins) and bacteriochlorophyll *a*, *b*, and *g* (bacteriochlorins) serve as the principal light-absorbing pigments in plant and bacterial photosynthetic systems, respectively.¹ Bonellin² and tolyporphins³ 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 B₁₂ and F₄₃₀) 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 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 total synthesis.⁹

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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_I*, F₄₃₀, and vitamin B₁₂). 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 of 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 dihydrodipyrin (**1**)¹⁰ and a tetrahydrodipyrin (**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 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 dihydrodipyrin 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 tetrahydrocorrin (**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 hydrodipyrins. In the chlorin synthesis,^{10–14} the pyrrole unit and the α -methyl pyrroline unit of the hydrodipyrin (Western half) both functioned as nucleophiles, the two complementary sites on the Eastern half (bromo-pyrrole, 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 hydrodipyrins with suitable reactivity at the α -position of the respective pyrrole or pyrroline unit.

A wide variety of dihydrodipyrin species bearing diverse α -substituents have been developed for syntheses of naturally occurring chlorins and isobacteriochlorins.^{16,17,19–29} (By contrast, the tetrahydrodipyrins 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 dihydrodipyrins (**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 **D**,^{20,21,23–26}), nucleophilic pyrrole (no α -substituent: **C**,¹⁷ **E**,²⁷ and **F**,²⁷ upon decarboxylation), nucleophilic pyrroline (α -methyl, which forms an enamine: **C**, **D**), 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*-oxide²² (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 dihydrodipyrins bear substituents at one or both β -pyrrole positions as required for synthesis of naturally occurring hydroporphyrins.

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 hydrodipyrryn precursors.

In this regard, the simple appearance of unsubstituted hydrodipyrrens 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-positions) 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 hydrodipyrrens can thwart a number of metal-mediated reactions. Perhaps less obviously, tetrahydrodipyrrens 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 hydrodipyrrens, particularly those lacking β -pyrrole substituents, is somewhat constrained.

In this paper, we describe the synthesis of new hydrodipyrrens, chiefly tetrahydrodipyrrens, with a variety of groups at the pyrrole and pyrroline α -positions. The emphasis on tetrahydrodipyrrens stems from studies in chlorin chemistry¹² where unsubstituted tetrahydrodipyrrens (e.g., **2**) were found to have a substantially longer shelf-life than the corresponding dihydrodipyrrens (e.g., **1**). The hydrodipyrrens 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 hydrodipyrrens are illustrated in Table 1. The hydrodipyrrens in each class differ in the pattern of reactivity (Nu^-/E^+) and number of C_1 synthons (0–2) attached at the 1- and 9-positions. While our chief focus centered on tetrahydrodipyrrens, we also examined dihydrodipyrrens and hexahydrodipyrrens to a limited extent. The following sections describe the routes that afforded the target compounds, protected analogues, and related derivatives.

2.2. Synthesis of hydrodipyrrens

(I) E^+/Nu^- Pyrroline-pyrrole units (0 α -carbons)

(i) 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** and 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 tetrahydrodipyrin **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.

(ii) Imidates: The electrophilicity of the α -pyrroline position can be altered by introduction of a leaving group. The synthesis of the corresponding tetrahydrodipyrin-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 (20% yield), or CsF in acetonitrile (10% yield). On the other hand, the use of TBAF in acetonitrile at room temperature gave **16** in 43% yield (see Experimental Section).

The reductive cyclization of nitroester **16** also was carried out under several conditions. Zn/HCO₂NH₄¹⁸ or Zn/AcOH¹² afforded the mixture of lactam **17** (9% or 30% yield) and hydroxamic acid **17-OH** (18% or 10% yield), respectively. The cleanest reaction and the highest yield were obtained with Zn/HCO₂H₃₂ in EtOH at room temperature, affording **17** in 45% yield. The reaction of **17** with trimethyloxonium tetrafluoroborate in anhydrous CH₂Cl₂ containing *N,N*-diisopropylethylamine (DIEA) provided the *O*-methylated product **14** in 50% yield (together with the *N*-methyl lactam **15** in 10% yield).

(iii) Thioimidates: The greater reactivity of thioesters and thioimidates versus the oxygen analogues^{23,33} towards nucleophilic substitution prompted the synthesis of tetrahydrodipyrin-thioimidates. Thus, treatment of lactam **17** with Lawesson's reagent³⁴ 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) carbonate²⁴ afforded the expected *S*-methylsulfanyl product **19** in 49% yield (Scheme 5).

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

(II) E⁺/Nu[−] Pyrroline-Pyrrole Units (1 α -Carbon)

(i) Hexahydrodipyrin-dithiane: The synthesis of the dithiane analogue (**20P**) of **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** did not give the desired nitropentanal-pyrrole **11**. 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 compound³⁷ 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 synthesis¹³ proved to be simpler and afforded a higher yield of **9-Ts** (55% versus 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 addition³⁸ 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 hexahydrodipyrin **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.

(ii) Tetrahydrodipyrin- and dihydrodipyrin-acetals: We examined the direct oxidation of the α -methyl group in pyrroline **2** to afford aldehyde **21** using SeO₂,²⁷ 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 tetrahydrodipyrin *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 SeO₂ 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-propanedithiol⁴¹ gave compound **25-Ts**, which was unstable (e.g., decomposed after 24 h in CDCl₃). 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 (**29-Ts**) using LaCl₃⁴⁴ 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 [MoO₂(acac)₂ in aqueous acetonitrile;⁴⁵ TFA/H₂O (3:1) in CH₂Cl₂^{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 tetrahydrodipyrin-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 DBU¹⁸ under solventless conditions provided **30** in 53% yield. Reductive cyclization of acetal **30** with Zn/HCO₂NH₄ in THF caused simultaneous reduction of the acetal to the methyl group, affording tetrahydrodipyrin **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 tetrahydrodipyrin-dimethyl acetal **21P**, albeit in very low yield.

To compare the reactivity of the tetrahydrodipyrin-acetal (**21P**) with that of a dihydrodipyrin-acetal (**32P**), we investigated the synthesis of the latter following the same method employed in the synthesis of dihydrodipyrin **1**.¹⁰ Jacobi *et al.* described a related diformyl-dihydrodipyrin (**C**; Chart 2),²⁷ but given the difficulties we encountered in preparing the 1-formyl-tetrahydrodipyrin **21**, we elected to prepare an acetal-protected analogue. Thus, reductive cyclization of **30** upon treatment with NaOMe followed by a buffered solution of TiCl₃ 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 dihydrodipyrin-acetal **32P** was more reactive than the tetrahydrodipyrin-acetal **21P** toward forming the corresponding bacteriochlorin (lacking any β -pyrrole substituents).⁴⁷

(iii) Tetrahydrodipyrin-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 previously⁴⁸ (Scheme 9).

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

(III) E^+/E^+ Pyrroline-pyrrole units (1 α -carbon)—The umpolung analogue of tetrahydrodipyrin **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** $\rightarrow$ **21**) was not viable, prompting examination of the *N*-oxide of tetrahydrodipyrin **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.

(IV) 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 $\text{Zn}/\text{NH}_4\text{Cl}$ provided tetrahydrodipyrin **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-dihydrodipyrin bearing substituents at both β -pyrrole positions.²⁷

(V) 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 tetrahydrodipyrin **2** with NBS proceeded selectively at the free α -pyrrole position, affording bromo-tetrahydrodipyrin **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.

(VI) Nu^-/E^+ Pyrroline-pyrrole units (2 α -carbons)—The tetrahydrodipyrin 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 $\text{Zn}/\text{HCO}_2\text{NH}_4$ 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 hydrodipyrins that have been developed over the years include (1) stepwise synthesis beginning with a pyrrole-2-carboxaldehyde and proceeding via nitroaldol condensation, reduction, Michael addition and metal-mediated reductive cyclization;^{16,17,20,22,23,30,49} (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 hydrodipyrin compounds.

Each new hydrodipyrin 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. Hydrodipyrins 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 tetrahydrodipyrins with diverse 1- and 9-substituents should facilitate a variety of studies concerning the synthesis of hydroporphyrins.

4. Experimental

4.1. General

¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra were collected at room temperature in CDCl₃ unless noted otherwise. Melting points are uncorrected. Column chromatography was performed with flash silica or alumina (80–200 mesh). The CHCl₃ contained 0.8% ethanol. THF was distilled from sodium benzophenone ketyl as required. CH₃CN was distilled from CaH₂ and stored over powdered molecular sieves. Other solvents were used as received.

4.2. Noncommercial 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-N¹¹-p-tosyldipyrin (2-Ts)—Following a procedure for the deoxygenation of *N*-oxides¹² with slight modification, TiCl₄ (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 LiAlH₄ (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 CH₂Cl₂. The organic layer was dried (Na₂SO₄) and concentrated. The resulting yellow oil was purified by column chromatography (silica, ethyl acetate) to give a pale yellow oil (76 mg, 75%): ¹H 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); ¹³C 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; FAB-MS obsd 345.1649, calcd 345.1637 [(M + H)⁺, M = C₁₉H₂₄N₂O₂S]. Anal. Calcd. for C₁₉H₂₄N₂O₂S: 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-dimethyldipyrin (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 (Na₂SO₄), and chromatographed [alumina, hexanes/ethyl acetate (3:1)] to give a pale yellow oil (64 mg, 34%): IR 3380, 2958 cm⁻¹; ¹H 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 (brs, 1H); ¹³C NMR δ 23.0, 27.4, 28.0, 40.3, 52.5, 80.9, 105.5, 107.5, 116.7, 131.5, 166.7; EI-MS obsd 176.1305, calcd 176.1313 (C₁₁H₁₆N₂).

4.3.3. *N*¹-tert-Butoxycarbonyl-3,3-dimethyl-2,3,4,5-tetrahydrodipyrin (6-Boc)—Following a general procedure,¹² TiCl₄ (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 LiAlH₄ (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 CH₂Cl₂. The organic layer was dried (Na₂SO₄), concentrated, and chromatographed (silica, ethyl acetate) to give a pale yellow oil (112 mg, 41%): IR 2958, 1740, 1333, 1126 cm⁻¹; ¹H 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); ¹³C 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; FAB-MS obsd 277.1917, calcd 277.1916 [(M + H)⁺, M = C₁₆H₂₄N₂O₂].

4.3.4. 3,3-Dimethyl-2,3,4,5-tetrahydro-*N*¹-*p*-tosyldipyrin (6-Ts)—Following a procedure for the deoxygenation of *N*-oxides¹² with slight modification, TiCl₄ (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 LiAlH₄ (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 CH₂Cl₂. The organic layer was dried (Na₂SO₄), 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; ¹H 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); ¹³C 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; FAB-MS obsd 331.1493, calcd 331.1480 [(M + H)⁺, M = C₁₈H₂₂N₂O₂S].

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 CH₂Cl₂ (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 CH₂Cl₂. The organic extract was dried (Na₂SO₄), concentrated, and chromatographed (silica, CH₂Cl₂) to give a light pink solid (10.7 g, 86%): mp 94–95 °C (lit. 37 mp 94–96 °C); ¹H 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); ¹³C 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 C₁₂H₁₁NO₃S: 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 CH₂Cl₂ (100 mL) and the resulting solution was washed with water. The organic extract was dried (Na₂SO₄), concentrated, and chromatographed (silica, CH₂Cl₂) to give a yellow solid (562 mg, 64%): mp 123–124 °C; IR 2965, 1748, 1504, 1368, 1331, 1123 cm⁻¹; ¹H 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); ¹³C NMR δ 28.2, 86.1, 112.4, 118.1, 126.3, 127.7, 130.1, 135.2, 148.7; FAB-MS obsd 239.1035, calcd 239.1032 [(M + H)⁺, M = C₁₁H₁₄N₂O₄]. Anal. Calcd. for C₁₁H₁₄N₂O₄: 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 CH₂Cl₂ (150 mL), and the resulting solution was washed with water. The organic extract was dried (Mg₂SO₄), concentrated, and chromatographed (silica, CH₂Cl₂) to give a yellow solid (18.3 g, 90%): mp 153–154 °C; ¹H 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); ¹³C 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 C₁₃H₁₂N₂O₄S: 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 CH₂Cl₂. The organic layer was dried (Na₂SO₄), concentrated, and chromatographed [silica, hexanes/CH₂Cl₂ (1:4)] to give a pale yellow oil (258 mg, 52%): IR 2980, 1736 cm⁻¹; ¹H 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); ¹³C NMR δ 27.1, 28.2, 75.0, 84.4, 110.5, 114.0, 122.2, 129.2, 149.5; FAB-MS obsd 240.1126, calcd 240.1110 (C₁₁H₁₆N₂O₄).

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 CH₂Cl₂ (100 mL) and washed with water. The organic layer was dried (Na₂SO₄), concentrated, and chromatographed [silica, hexanes/CHCl₃ (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 evaporated under reduced pressure. The residue was dissolved in CH₂Cl₂ (150 mL) and washed with water. The organic layer was dried (Na₂SO₄), concentrated, and chromatographed [silica, hexanes/CH₂Cl₂ (3:7)] to give a light yellow solid (1.64 g, 31%); mp 95–96 °C; ¹H 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); ¹³C 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 C₁₃H₁₄N₂O₄S: 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 CH₂Cl₂ (100 mL) and washed with water. The organic layer was dried (Na₂SO₄), concentrated, and chromatographed [silica, CH₂Cl₂/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; ¹H NMR δ 1.24 (s, 3H), 1.29 (s, 3H), 1.59 (s, 9H), 2.49–2.61 (m, 2H), 3.38 (ABX, ³*J* = 11.6 Hz, ²*J* = 15.2 Hz, 1H), 3.58 (ABX, ³*J* = 2.0 Hz, ²*J* = 15.2 Hz, 1H), 4.92 (ABX, ³*J* = 2.0 Hz, ³*J* = 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); ¹³C 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; FAB-MS obsd 325.1759, calcd 325.1763 [(M + H)⁺, M = C₁₆H₂₄N₂O₅]. Anal. Calcd. for C₁₆H₂₄N₂O₅: 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 cooling 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%): ^1H 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 $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_5\text{S}$: 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-dimethyldipyrin *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; $\text{CH}_2\text{Cl}_2 \rightarrow$ 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} ; ^1H 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; FAB-MS obsd 293.1875, calcd 293.1865 [(M + H)⁺, M = $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_3$].

4.3.15. 2,3,4,5-Tetrahydro-3,3-dimethyl-*N*¹¹-*p*-tosyldipyrin *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%): ^1H 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; FAB-MS obsd 347.1420, calcd 347.1429 [(M + H)⁺, M = $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_3\text{S}$].

4.3.16. 2,3,4,5-Tetrahydro-3,3-dimethyldipyrin *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} ; ^1H 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 (brs, 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; EI-MS obsd 192.1265, calcd 192.1263 ($\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}$).

4.3.17. 2,3,4,5-Tetrahydro-1-methoxy-3,3-dimethyldipyrin (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 CH₂Cl₂ (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 CH₂Cl₂ (10 mL), washed (water and brine), dried (Na₂SO₄) 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-trimethyldipyrin-1(10*H*)-one (**15**) (14 mg, 10%). Data for **14**: mp 85–88 °C; ¹H NMR δ 1.02 (s, 3H), 1.14 (s, 3H), 2.25 (AB, ²*J* = 16.4 Hz, 1H), 2.41 (AB, ²*J* = 16.4 Hz, 1H), 2.58 (ABX, ³*J* = 11.6, ²*J* = 14.8, 1H), 2.77 (ABX, ³*J* = 2.6 Hz, ²*J* = 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 (brs, 1H); ¹³C 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; FAB-MS obsd 207.1498, calcd 207.1497 [(M + H)⁺, M = C₁₂H₁₈N₂O]. Data for **15**: mp 92–95 °C; ¹H NMR δ 1.01 (s, 3H), 1.10 (s, 3H), 2.02 (AB, ²*J* = 16.2 Hz, 1H), 2.22 (AB, ²*J* = 16.2 Hz, 1H), 2.55 (s, 3H), 2.73 (ABX, ³*J* = 8.4 Hz, ²*J* = 14.8 Hz, 1H), 2.90 (ABX, ³*J* = 5.4 Hz, ²*J* = 14.8 Hz, 1H), 3.28 (ABX, ³*J* = 5.4 Hz, ³*J* = 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 (brs, 1H); ¹³C 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. FAB-MS obsd 207.1498, calcd 207.1497 [(M + H)⁺, M = C₁₂H₁₈N₂O]. Anal. Calcd for C₁₂H₁₈N₂O: 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-pyrrolyl)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 (Na₂SO₄) 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%): ¹H NMR δ 1.16 (s, 3H), 1.21 (s, 3H), 2.42 (s, 2H), 3.10 (ABX, ³*J* = 2.4 Hz, ²*J* = 15.4 Hz, 1H), 3.37 (ABX, ³*J* = 11.6 Hz, ²*J* = 15.4 Hz, 1H), 3.72 (s, 3H), 4.94 (ABX, ³*J* = 11.6 Hz, ³*J* = 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 (brs, 1H); ¹³C 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; FAB-MS obsd 255.1336, calcd 255.1345 [(M + H)⁺, M = C₁₂H₁₈N₂O₄].

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 CH₃CN (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 (Na₂SO₄) 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 (¹H NMR, ¹³C NMR, and FAB-MS) 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 mmol, 3.0 mol equiv, freshly dried by heating at 100 °C under vacuum for 1 h and then cooling 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 mmol, 10.0 mol equiv) in CH₃CN (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 (^1H NMR, ^{13}C NMR, and FAB-MS) 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 procedure²³ with slight modification, nitroethylpyrrole **9** (4.20 g, 30.0 mmol) and powdered molecular sieves 4Å (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 (^1H NMR, ^{13}C NMR, and FAB-MS) were consistent with those obtained from samples prepared via the solventless method.

4.3.22. 2,3,4,5-Tetrahydro-3,3-dimethyldipyrin-1(10H)-one (17) via Zn/HCO₂NH₄—Following a general procedure,¹⁸ a solution of **16** (0.153 g, 0.600 mmol) in ethanol (1.2 mL) was treated with HCO₂NH₄ (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-dimethyldipyrin (**17-OH**) (23 mg, 18%). Data for **17**: mp 92–94 °C; ^1H 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 (brs, 1H), 5.94–6.20 (m, 1H), 6.14–6.16 (m, 1H), 6.69–6.71 (m, 1H), 8.10–8.25 (brs, 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; FAB-MS obsd 193.1337, calcd 193.1341 [(M + H)⁺, M = C₁₁H₁₆N₂O]. Data for **17-OH**: mp 120–122 °C; ^1H 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 (brs, 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; FAB-MS obsd 209.1291, calcd 209.1290 [(M + H)⁺, M = C₁₁H₁₆N₂O₂].

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 NaHCO₃, 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, ^1H NMR, ^{13}C NMR, and FAB-MS) were consistent with those obtained from samples prepared via reduction with Zn/HCO₂NH₄.

4.3.24. Synthesis of 17 via Zn/HCO₂H—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 NaHCO₃, washed (water and brine), dried (Na₂SO₄) 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, ¹H NMR, ¹³C NMR, and FAB-MS) were consistent with those obtained from samples prepared via reduction with Zn/HCO₂NH₄.

4.3.25. 2,3,4,5-Tetrahydro-3,3-dimethyldipyrin-1(10H)-thione (18)—Following a general procedure²⁴ 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, CH₂Cl₂/ethyl acetate (5:3)] to afford a white solid (0.029 g, 43%): mp 105–108 °C; ¹H 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 (brs, 1H), 8.02–8.18 (brs, 1H); ¹³C NMR δ 22.4, 26.8, 28.2, 41.3, 58.4, 70.7, 107.0, 109.4, 118.0, 127.3, 204.9; FAB-MS obsd 209.1103, calcd 209.1112 [(M + H)⁺, M = C₁₁H₁₆N₂S].

4.3.26. 2,3,4,5-Tetrahydro-1-methylsulfanyl-3,3-dimethyldipyrin (19)—Following a reported procedure,²⁴ a solution of **18** (0.023 g, 0.11 mmol) in THF (3 mL) was treated first with Ag₂CO₃ (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 NaHCO₃, 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; ¹H 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 (brs, 1H); ¹³C 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; FAB-MS obsd 223.1263, calcd 223.1269 [(M + H)⁺, M = C₁₂H₁₈N₂S].

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 CH₂Cl₂. The organic extract was dried (Na₂SO₄), concentrated, and chromatographed (silica, ethyl acetate) to give a colorless oil (27 mg, 47%): ¹H 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 (brs, 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 (brs, 1H); ¹³C 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; FAB-MS obsd 297.1462, calcd 297.1459 [(M + H)⁺, M = C₁₅H₂₄N₂S₂].

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 CH₂Cl₂. The organic extract was dried (Na₂SO₄), concentrated, and chromatographed (silica, ethyl acetate) to give a light brown solid (61 mg, 44%): mp 108–110 °C; ¹H 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 (brs, 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; FAB-MS obsd 297.1466, calcd 297.1459 [(M + H) $^+$, M = C₁₅H₂₄N₂S₂].

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 addition of saturated aqueous NH₄Cl (20 mL). The mixture was extracted with CH₂Cl₂. The organic extract was dried (Na₂SO₄) and concentrated. TLC analysis [silica, ethyl acetate/hexanes (9:1)] showed two components with $R_f = 0.67$ (**20aP-Ts**, minor) and $R_f = 0.47$ (**20bP-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; ^1H 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; FAB-MS obsd 451.1540, calcd 451.1548 [(M + H) $^+$, M = C₂₂H₃₀N₂O₂S₃]. Anal. Calcd. for C₂₂H₃₀N₂O₂S₃: 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; ^1H 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 (brs, 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; FAB-MS obsd 451.1556, calcd 451.1548 [(M + H) $^+$, M = C₂₂H₃₀N₂O₂S₃].

4.3.30. 1-(Dimethoxymethyl)-2,3,4,5-tetrahydro-3,3-dimethyldipyrin (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 (Na₂SO₄), concentrated, and chromatographed [silica, CH₂Cl₂/ethyl acetate (4:1)] to give a colorless oil (131 mg, 43%): ^1H 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 (brs, 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; FAB-MS obsd 251.1753, calcd 251.1760 [(M + H) $^+$, M = C₁₄H₂₂N₂O₂].

4.3.31. 1-(Dimethoxymethyl)-2,3,4,5-tetrahydro-3,3-dimethyldipyrin (21P) from **31**—

Following a general procedure,¹² a sample of TiCl₄ (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 LiAlH₄ (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 CH₂Cl₂ and ethyl acetate. The organic extract was washed with water, dried (Na₂SO₄) and chromatographed [silica, CH₂Cl₂/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*¹-*p*-tosyldipyrin (21P-Ts)—Following a general procedure,¹² TiCl₄ (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 LiAlH₄ (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 CH₂Cl₂ and ethyl acetate. The organic extract was washed with water, dried (Na₂SO₄), and chromatographed [silica, CH₂Cl₂/ethyl acetate (4:1)] to give a colorless oil (525 mg, 84%): ¹H NMR δ 0.90 (s, 3H), 1.08 (s, 3H), 2.40 (s, 3H), 2.37–2.49 (m, 2H), 2.72 (ABX, ³*J* = 9.6 Hz, ²*J* = 16.0 Hz, 1H), 2.98 (ABX, ³*J* = 4.8 Hz, ²*J* = 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); ¹³C 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; FAB-MS obsd 405.1840, calcd 405.1848 [(M + H)⁺, M = C₂₁H₂₈N₂O₄S]. Anal. Calcd. for C₂₁H₂₈N₂O₄S: 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 cooling 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; ¹H 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); ¹³C 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 C₁₉H₂₄N₂O₅S: 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*¹-*p*-tosyldipyrin *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, CH₂Cl₂/ethyl acetate (1:1) → CH₂Cl₂/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; ¹H 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 $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_3\text{S}$: 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} ; ^1H NMR δ 1.06 (s, 3H), 1.10 (s, 3H), 2.41 (s, 3H), 2.57–2.59 (m, 2H), 3.06 (ABX, $^3J = 9.2$ Hz, $^2J = 16.0$ Hz, 1H), 3.43 (ABX, $^3J = 4.4$ Hz, $^2J = 16.0$ 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 $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_4\text{S}$: 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 $\text{BF}_3\cdot\text{OEt}_2$ (140 μL , 1.1 mmol) and powdered molecular sieves (4 Å, ~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 (~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%): ^1H 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; ^1H 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, $^3J = 10.0$ Hz, $^2J = 16.0$ Hz, 1H), 3.45 (ABX, $^3J = 3.6$ Hz, $^2J = 16.0$ 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; FAB-MS obsd 461.2100, calcd 461.2110 [(M + H)⁺, M = $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_5\text{S}$].

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 LiAlH₄ (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 CH₂Cl₂ and ethyl acetate. The organic extract was washed with water, dried (Na₂SO₄), and chromatographed [silica, CH₂Cl₂/ethyl acetate (19:1)] to give a colorless oil (116 mg, 92%): ¹H 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); ¹³C 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; FAB-MS obsd 445.2152, calcd 445.2161 [(M + H)⁺, M = C₂₄H₃₂N₂O₄S].

4.3.39. 1-(Dimethoxymethyl)-2,3,4,5-tetrahydro-3,3-dimethyl-*N*¹-*p*-tosyldipyrin *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 LaCl₃·H₂O (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 NaHCO₃ (16 mL). The mixture was extracted with ethyl acetate. The organic extract was dried (Na₂SO₄), concentrated, and chromatographed [silica, CH₂Cl₂/ethyl acetate (4:1)] to afford a white solid (180 mg, 56%): mp 108–109 °C; ¹H 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); ¹³C 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 C₂₁H₂₈N₂O₅S: 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 cooling 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, CH₂Cl₂) gave a light brown solid (1.99 g, 34%): mp 74–75 °C; ¹H NMR δ 1.14 (s, 3H), 1.23 (s, 3H), 2.60, 2.72 (AB, ²J = 18.6 Hz, 2H), 3.03 (ABX, ³J = 2.4 Hz, ²J = 15.6 Hz, 1H), 3.36 (ABX, ³J = 11.8 Hz, ²J = 15.6 Hz, 1H), 3.43 (s, 3H), 3.44 (s, 3H), 4.36 (s, 1H), 5.15 (ABX, ³J = 2.4 Hz, ³J = 11.8 Hz, 1H), 5.97–5.99 (m, 1H), 6.08–6.11 (m, 1H), 6.65–6.67 (m, 1H), 8.00–8.13 (brs, 1H); ¹³C 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; FAB-MS obsd 299.1605, calcd 299.1607. Anal. Calcd for C₁₄H₂₂N₂O₅: 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 CH₂Cl₂. The mixture was washed with water and brine. The organic layer was dried (Na₂SO₄), concentrated, and chromatographed (silica, CH₂Cl₂) 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-dimethyldipyrin 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, CH₂Cl₂/ethyl acetate (9:1)] to afford a white solid (9.0 mg, 17%): mp 68–70 °C; ¹H 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 (brs, 1H); ¹³C 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; FAB-MS obsd 266.1630, calcd 266.1630 (M = C₁₄H₂₂N₂O₃).

4.3.43. 2,3-Dihydro-1-(dimethoxymethyl)-3,3-dimethyldipyrin (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. TiCl₃ (8.6 wt% TiCl₃ 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 TiCl₃ 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 NaHCO₃ (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%): ¹H 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 (brs, 1H); ¹³C 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} (CH₂Cl₂) 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*-tosyldipyrin 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 addition of H₂O/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; ¹H NMR δ 0.89 (s, 3H), 1.01 (s, 3H), 2.18, 2.32 (AB, ²J = 17.6 Hz, 2H), 2.40 (s, 3H), 3.07 (ABX, ³J = 9.8 Hz, ²J = 15.8 Hz, 1H), 3.47 (ABX, ³J = 4.2 Hz, ²J = 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 (brs, 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); ¹³C 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; FAB-MS obsd 453.1854, calcd 453.1848 (C₂₅H₂₈N₂O₄S). Data for **33b-Ts**: mp 156–158 °C; ¹H NMR δ 0.96 (s, 3H), 0.97 (s, 3H), 2.23–2.26 (m, 2H), 2.40 (s, 3H), 3.15 (ABX, ³J = 9.8 Hz, ²J = 16.0 Hz, 1H), 3.48 (ABX, ³J = 4.0 Hz, ²J = 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); ¹³C 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; FAB-MS obsd 453.1859, calcd 453.1848 (C₂₅H₂₈N₂O₄S).

4.3.45. 9-Bromo-2,3,4,5-tetrahydro-1,3,3-trimethyldipyrin N¹⁰-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 $124\text{--}125^{\circ}\text{C}$ (dec.); ^1H NMR δ 1.09 (s, 3H), 1.19 (s, 3H), 2.07–2.08 (m, 3H), 2.32, 2.48 (AB, $^2J = 17.6$ Hz, 2H), 2.91 (ABX, $^3J = 2.8$ Hz, $^2J = 15.6$ Hz, 1H), 3.00 (ABX, $^3J = 7.2$ Hz, $^2J = 15.6$ Hz, 1H), 3.84–3.91 (m, 1H), 5.85–5.87 (m, 1H), 5.96–5.98 (m, 1H), 10.92–11.03 (brs, 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 $\text{C}_{12}\text{H}_{17}\text{BrN}_2\text{O}$: 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-dimethyldipyrin N¹⁰-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 $115\text{--}117^{\circ}\text{C}$ (dec.); ^1H NMR δ 1.09 (s, 3H), 1.27 (s, 3H), 2.60 (AB, $^2J = 17.2$ Hz, 1H), 2.66 (AB, $^2J = 17.2$ Hz, 1H), 2.84 (ABX, $^3J = 2.2$ Hz, $^2J = 16.0$ Hz, 1H), 3.08 (ABX, $^3J = 8.2$ Hz, $^2J = 16.0$ Hz, 1H), 4.06–4.11 (m, 1H), 5.88–5.90 (m, 1H), 5.99–6.01 (m, 1H), 9.64–9.74 (brs, 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; FAB-MS obsd 299.0385, calcd 299.0395 [(M + H)⁺, M = $\text{C}_{12}\text{H}_{15}\text{BrN}_2\text{O}_2$].

4.3.47. 6-(5-Formylpyrrol-2-yl)-1,1-dimethoxy-4,4-dimethyl-5-nitrohexan-2-one (36)—

A sample of **30** (0.289 g, 1.00 mmol) was dissolved in CH_2Cl_2 (2 mL) and DMF (1 mL) was added. The resulting solution 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 $103\text{--}104^{\circ}\text{C}$; ^1H NMR δ 1.16 (s, 3H), 1.26 (s, 3H), 2.64 (AB, $^2J = 18.4$ Hz, 1H), 2.72 (AB, $^2J = 18.4$ Hz, 1H), 3.16 (ABX, $^3J = 2.4$ Hz, $^2J = 15.2$ Hz, 1H), 3.42 (s, 3H), 3.43 (s, 3H), 3.45 (m, overlapped, 1H), 4.35 (s, 1H), 5.23 (ABX, $^3J = 2.4$ Hz, $^2J = 11.6$ Hz, 1H), 6.10–6.11 (m, 1H), 6.86–6.88 (m, 1H), 6.38 (s, 1H), 10.42–10.46 (br, 1H); ^{13}C 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; FAB-MS obsd 327.1569, calcd 327.1556 [(M + H)⁺, M = $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_6$].

4.3.48. 9-Formyl-2,3-dihydro-1-(dimethoxymethyl)-3,3-dimethyldipyrin (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 $69\text{--}71^{\circ}\text{C}$; ^1H NMR δ 1.09, (s, 3H), 1.20 (s, 3H), 2.44–2.56 (m, 2H), 2.98 (ABX, $^3J = 3.2$ Hz, $^2J = 16.0$ Hz, 1H), 3.14 (ABX, $^3J = 7.8$ Hz, $^2J = 16.0$ 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, 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; FAB-MS obsd 279.1696, calcd 279.1709 (M = $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_3$).

4.3.49. 9-Bromo-2,3,4,5-tetrahydro-1,3,3-trimethyldipyrin (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 $102\text{--}104^{\circ}\text{C}$ (dec.); ^1H 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 (brs, 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; FAB-MS obsd 269.0641, calcd 269.0653 [(M + H)⁺, M = $\text{C}_{12}\text{H}_{17}\text{BrN}_2$].

4.3.50. 9-Formyl-2,3,4,5-tetrahydro-1,3,3-trimethyldipyrin (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 $72\text{--}74^{\circ}\text{C}$; ^1H 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 (brs, 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; FAB-MS obsd 219.1491, calcd 219.1497 [(M + H)⁺, M = $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}$].

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 in 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, ^1H NMR, ^{13}C NMR, and FAB-MS) were consistent with those obtained from samples prepared via an earlier route. Data for **42**: ^1H 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 (brs, 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; FAB-MS obsd 247.1439, calcd 247.1447 [(M + H)⁺, M = $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_2$].

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 in 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; ^1H 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 (brs, 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; FAB-MS obsd 267.1353, calcd 267.1345 [(M + H)⁺, M = C₁₃H₁₈N₂O₄]. Data for **40'**: mp 182–185 °C; ^1H 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 (brs, 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; FAB-MS obsd 249.1226, calcd 249.1239 [(M + H)⁺, M = C₁₃H₁₆N₂O₃].

4.3.53. 2,3,4,5-Tetrahydro-1,3,3,9-tetramethyldipyrin N-oxide (41)—Following a general procedure,¹² a vigorously stirred solution of **40** (0.26 g, 1.00 mmol) in acetic acid (5.0 mL) and ethanol (5 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 NaHCO₃, washed (water and brine), dried (Na₂SO₄) 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; ^1H 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 (brs, 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; FAB-MS obsd 220.1562, calcd 220.1567 (C₁₃H₂₀N₂O).

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Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.

Scheme 6.

Scheme 7.

Scheme 8.

Scheme 9.

Scheme 10.

Scheme 11.

Scheme 12.

Scheme 13.

Chart 1.

Chart 2.

Table 1

Target hydrodipyrins

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)