JOC The Journal of Organic Chemistry
Cite This: J. Org. Chem. 2019, 84, 11286−11293
Note
pubs.acs.org/joc

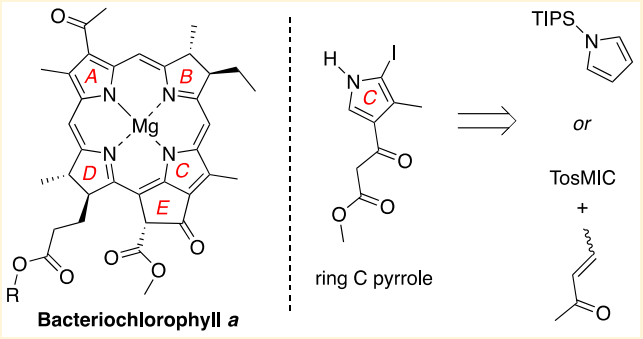
Synthesis of the Ring C Pyrrole of Native Chlorophylls and Bacteriochlorophylls

Pengzhi Wang,[†] Khiem Chau Nguyen,[†] and Jonathan S. Lindsey*

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

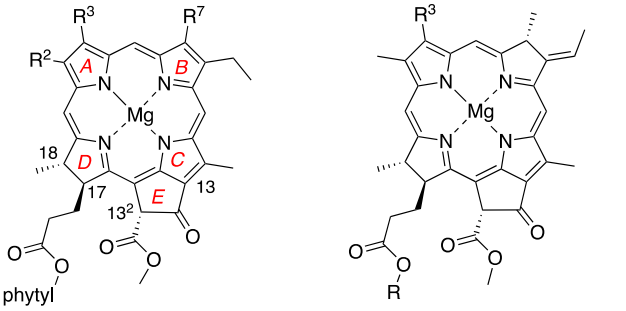
Supporting Information

ABSTRACT: As part of a program to develop practical syntheses of members of the family of (bacterio)chlorophylls, two routes to 2-iodo-3-methyl-4-(3-methoxy-1,3-dioxopropyl)pyrrole, a precursor of the universal ring C, have been developed. The β-ketoester of ring C is expected to give rise to ring E upon Knoevenagel condensation and Nazarov cyclization with a ring D constituent as demonstrated in an analogue synthesis. Two viable routes were developed beginning with *N*-TIPS-pyrrole or with 4-oxo-2-pentene and TosMIC, affording multi-gram-quantities of this ostensibly simple pyrrole.



The photosynthetic tetrapyrroles are some of Nature's most valuable and abundant molecules yet have largely escaped the attention of the synthetic chemistry community.[1] The most prevalent such tetrapyrroles include the chlorophylls (in plants and cyanobacteria) and bacteriochlorophylls (in anoxygenic photosynthetic bacteria). Representative structures are shown in Chart 1.[2] Chlorophylls *a*, *b*, *d*, and *f* each contain one pyrroline unit (ring D) and vary only in the nature of auxochromes (vinyl, formyl) at positions 2, 3, and 7. Bacteriochlorophylls *a*, *b*, and *g* each contain two pyrroline units (rings B and D) and vary in the nature of the 3-substituent (vinyl, acetyl), the pyrroline 8-substituent, and the hydrocarbon (phytyl, farnesyl) at the 17[3] ester position.

Chart 1. Structures of Predominant Chlorophylls and Bacteriochlorophylls



Chl *a* ($R^{2,7}$ = Me, R^3 = vinyl)
Chl *b* (R^2 = Me, R^3 = vinyl, R^7 = CHO)
Chl *d* ($R^{2,7}$ = Me, R^3 = CHO)
Chl *f* (R^2 = CHO, R^3 = vinyl, R^7 = Me)

Bchl *b* (R^3 = acetyl, R = phytyl)
Bchl *g* (R^3 = vinyl, R = farnesyl)

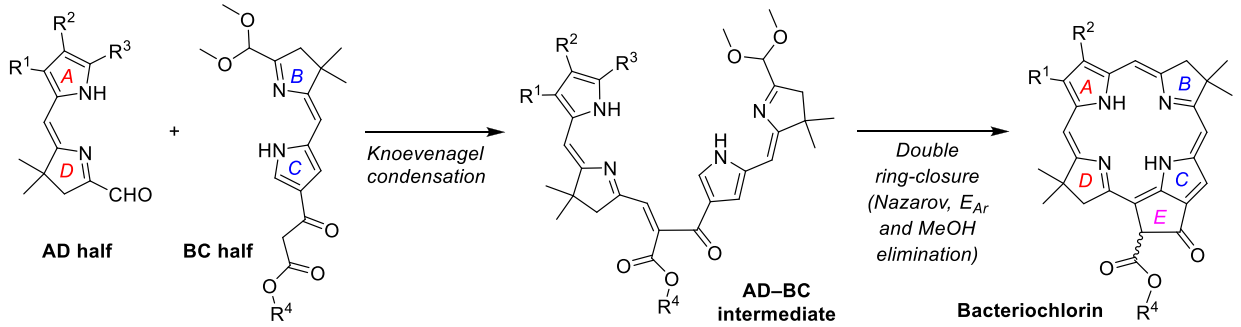
We recently described the *de novo* construction of the full skeleton of bacteriochlorophyll analogues by the directed joining of two dihydrodipyrrins (Scheme 1).[3] Each dihydrodipyrrin bears a gem-dimethyl group in the pyrroline ring,[4] which is distinct from the *trans*-dialkyl or alkyl/alkenyl substituents of the native pigments. The BC dihydrodipyrrin is equipped with an acetal and an open pyrrole position at the two α-termini, as well as a β-ketoester (hereafter termed 3-methoxy-1,3-dioxopropyl) at the pyrrole β-position flanking the α-site. The AD dihydrodipyrrin bears a carboxaldehyde group and an open pyrrole position (or R^3 = *tert*-butyloxycarbonyl) at the two α-termini. The two halves are joined via Knoevenagel condensation. A subsequent one-flask process entails Nazarov cyclization to form the isocyclic ring (ring E), electrophilic aromatic substitution to form the macrocycle, and elimination of methanol to yield the aromatic bacteriochlorin.

We have begun working to extend the route shown in Scheme 1 to accommodate the substituents and stereochemical features characteristic of the native pigments, particularly bacteriochlorophylls, which apparently have never been the object of synthesis. While the substituents in rings A and B vary across the family of (bacterio)chlorophylls, the respective substituents in rings C and D are largely invariant. An immediate target is ring C, the synthesis of which should be applicable to the entire family of (bacterio)chlorophylls. The ring C pyrrole bears methyl and 3-methoxy-1,3-dioxopropyl groups at the respective 3- and 4-positions, no substituent at the 5-position, and iodo at the 2-position (for Pd-mediated coupling to form the BC dihydrodipyrrin).

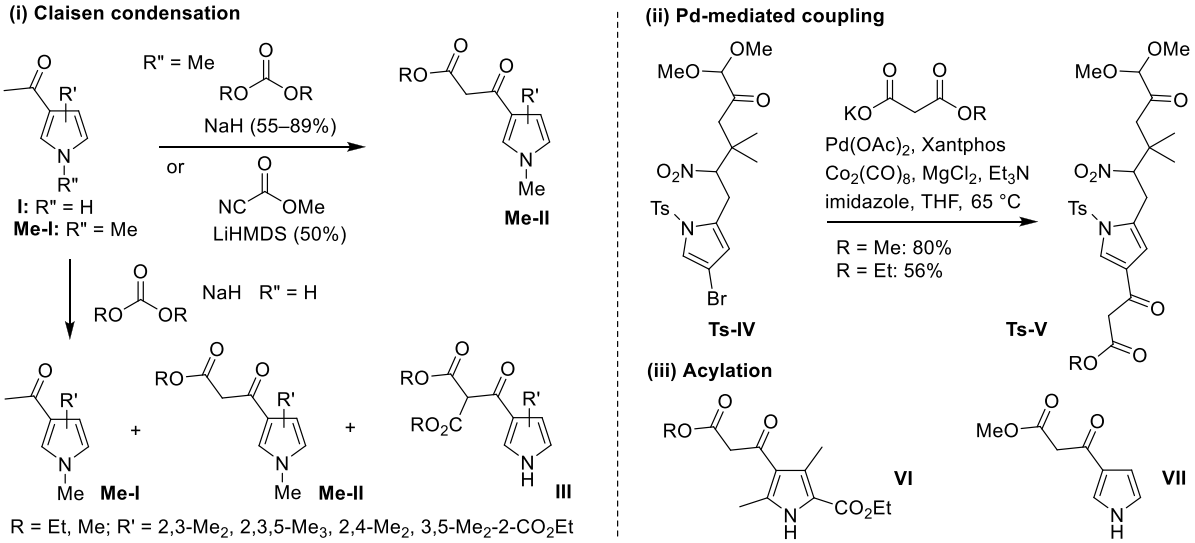
Received: June 20, 2019
Published: August 21, 2019

DOI: 10.1021/acs.joc.9b01650
J. Org. Chem. 2019, 84, 11286−11293

Scheme 1. *De Novo* Synthesis of the Full Skeleton of Bacteriochlorophylls



Scheme 2. Prior Approaches to Pyrroles Bearing a 3-Alkoxy-1,3-dioxopropyl Substituent



A key objective has been to obtain ≥10 mmol of the ring C pyrrole in a straightforward manner from readily available precursors. While a seemingly simple objective, we ultimately investigated ∼10 synthetic approaches. Formation of the 3-methoxy-1,3-dioxopropyl group at the pyrrole α-position is straightforward from 2-acetylpyrrole,[5−7] but the pyrrole β-position presents significant challenges particularly in the face of open α-positions and an unsubstituted and unhindered nitrogen atom. Results illustrating this methodological lacuna are as follows:

(i) Claisen condensation of β-acetylpyrroles with dialkyl carbonates[8] or methyl cyanoformate[9] was successful with *N*-substituted substrates (**Me-I** → **Me-II**, Scheme 2), but *N*-unsubstituted pyrroles (**I**) yielded unwanted products due to *N*-alkylation (**Me-I**, **Me-II**) and further reaction of the pyrrole-attached 3-methoxy-1,3-dioxopropyl moiety (**III**).[8]

(ii) Pd-mediated carbonylation[3] or alkoxycarbonylation[10] enabled formation of the 3-methoxy-1,3-dioxopropyl unit in fair to good yields (**Ts-IV** → **Ts-V**)[3] but has been demonstrated only for *N*-substituted pyrroles.

(iii) Acylation of a malonate with a pyrrole acid chloride, or of a pyrrole with a malonyl chloride, is restricted to deactivated pyrroles with a full complement of substituents (affording, e.g., **VI**).[8,11−13]

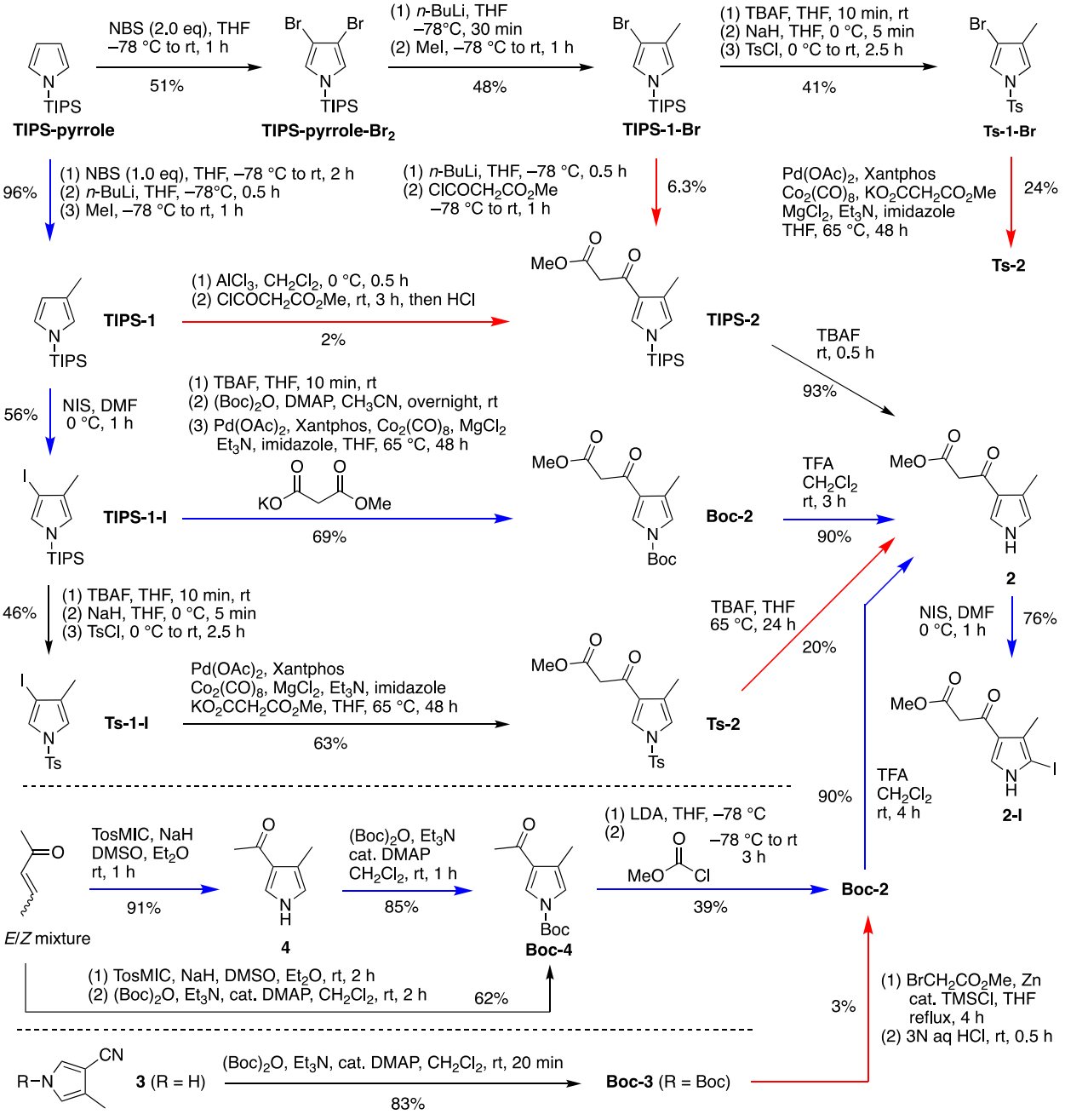
(iv) Pyrrole **VII** was used in pioneering studies of Nazarov cyclization,[5−7] but procedure, scale, and characterization data were not provided for the stated synthesis from 3-carboxypyrrole[5,6] or 3-acetylpyrrole.[7]

Given the objective of a scalable synthesis and awareness of the potent effects of a single methyl group on the reactivity of pyrroles,[14,15] we investigated routes beginning with the commercially available **TIPS-pyrrole** (Scheme 3). The direct Friedel−Crafts acylation of known *N*-TIPS-3-methylpyrrole **TIPS-1**[16] (obtained from **TIPS-pyrrole** in 96% yield by β-monobromination, lithium−bromine exchange, and methylation) with methyl malonyl chloride and $AlCl_3$ gave **TIPS-2** in only 2% yield. The classic halogen−lithium exchange reaction of TIPS-protected pyrrole **TIPS-1-Br**[17] (available from **TIPS-pyrrole-Br$_2$**[18]) with methyl malonyl chloride gave **TIPS-2** in 6.3% yield, although subsequent deprotection with TBAF afforded **2** in 93% yield.

The direct carbonylation of **TIPS-1-Br** was attempted with $Co_2(CO)_8$ and methyl potassium malonate under standard conditions ($Pd(OAc)_2$, Xantphos, $MgCl_2$, Et_3N, and imidazole in THF at reflux for 48 h),[3] but **TIPS-2** was not obtained (not shown), even though the identical conditions afforded good conversion of **Ts-IV** to **Ts-V** (Scheme 2). Moreover, 50% of starting material still remained, which indicated the low reactivity of **TIPS-1-Br**. Cleavage of the TIPS group with TBAF followed by tosylation with NaH/TsCl afforded **Ts-1-Br** in 41% yield. The Pd-catalyzed reaction of **Ts-1-Br** gave *p*-tosyl-protected **Ts-2** in 24% yield.

DOI: 10.1021/acs.joc.9b01650
J. Org. Chem. 2019, 84, 11286−11293

Scheme 3. Most Suitable Routes to 2-I Are Shown with Blue Arrows; Limiting Steps in Other Approaches Are Illustrated with Red Arrows



To ameliorate the direct, Pd-mediated installation of the 3-methoxy-1,3-dioxopropyl unit, **TIPS-1** was iodinated with NIS to give **TIPS-1-I**[19] (56% yield), which was then treated via the same sequence of TIPS removal and *N*-tosylation as for **TIPS-1-Br** to give **Ts-1-I**. The single-crystal X-ray structures of **Ts-1-Br** and **Ts-1-I** (Supporting Information) confirmed the substituent positions in the respective pyrroles. The direct Pd-mediated reaction[3] of **Ts-1-I** with methyl potassium malonate and $Co_2(CO)_8$ afforded **Ts-2** in 63% yield, to be compared with the 24% yield for the bromo substrate **Ts-1-Br**. While promising, cleavage of the *p*-tosyl group of **Ts-2** in the presence of 8.4 equiv of TBAF at 65 °C for 24 h afforded free pyrrole **2** in only 20% yield.

An improved approach from **TIPS-1-I** entailed replacement of TIPS with Boc followed by Pd-mediated carbonylation with methyl potassium malonate and $Co_2(CO)_8$ to afford **Boc-2** in 69% yield. Cleavage of the Boc group with TFA in CH_2Cl_2 gave **2** in 90% yield. We note that treatment of **TIPS-1-I** to direct carbonylation resulted in consumption of all starting material, but again without formation of **TIPS-2**. In summary, the TIPS group enables installation of the 3-methyl and 4-iodo substituents whereas the Boc group is superior to the Ts group in the subsequent carbonylation: the conversion of **TIPS-pyrrole** via **TIPS-1**, **TIPS-1-I**, and **Boc-2** afforded **2** (0.49 g, 1.7 mmol) in 33% overall yield.

In pursuit of a more concise route, we shifted our attention to pyrroles bearing a cyano or acetyl substituent for elaboration

DOI: 10.1021/acs.joc.9b01650
J. Org. Chem. 2019, 84, 11286–11293

to the 3-methoxy-1,3-dioxopropyl unit. 3-Cyano-4-methylpyrrole (**3**),[20] prepared from crotononitrile and TosMIC and fully characterized here, gave no product in the Blaise reaction[21] with methyl bromoacetate in the presence of zinc metal. The *N*-Boc analogue **Boc-3** gave the desired product but in only 3% yield.

The van Leusen reaction[22,23] of 4-oxo-2-pentene with TosMIC afforded 3-acetyl-4-methylpyrrole (**4**[20]) in 91% yield. The absence of *N*-protection in **4** led to side reactions upon treatment with dimethyl carbonate or methyl chloroformate, affording chiefly the putative *N*-methylpyrrole **Me-2** or *N*-methoxycarbonylpyrrole **MeO_2C-4**, respectively. Analogous side products were reported by Kenner and co-workers upon similar treatment of 3-acetylpyrroles.[8] Attempted carbonylation of TIPS-protected 3-acetylpyrrole (**TIPS-4**, prepared by *N*-silylation[24] of **4**) with dimethyl carbonate or methyl chloroformate again afforded side products from reaction at the nitrogen center. To sidestep the desilylation under the reaction conditions, *N*-Boc-4-acetyl-3-methylpyrrole (**Boc-4**,[25] prepared by a new procedure[26]) was examined. While analogous reactions of **Boc-4** failed with NaH, KH, or LiHMDS, use of LDA afforded the 3-methoxy-1,3-dioxopropyl-containing **Boc-2** in 39% yield. Treatment of **Boc-2** with TFA afforded pyrrole **2** in 90% yield. Attempts to obtain **2** by the direct van Leusen reaction with methyl 3-oxo-4-hexenonate gave no pyrrole, likely due to the greater acidity of methyl 3-oxo-4-hexenonate versus TosMIC, thereby impeding the required deprotonation of TosMIC. In summary, the 4-step synthesis beginning with 4-oxo-2-pentene and TosMIC afforded pyrrole **2** (6.16 g, 34 mmol) in 27% overall yield.

The acyl moiety of the 4-(3-methoxy-1,3-dioxopropyl) group serves as a directing group for electrophilic aromatic substitution at the pyrrole 2-position. Thus, treatment of **2** with 1.0 equiv of *N*-iodosuccinimide in anhydrous DMF at 0 °C (at 0.076 M, a concentration lower than that of a general procedure[27]) afforded α-iodinated pyrrole **2-I** in 76% yield (7.92 g, ∼25 mmol). Halogenated pyrroles can be quite unstable,[28] but the presence of a single acyl group imparts substantial stability, and in this regard, **2-I** has proven to be stable for at least several months upon storage at −20 °C.

In summary, two routes have been developed for access to 2-iodo-3-methyl-4-(3-methoxy-1,3-dioxopropyl)pyrrole. Both routes require *N*-protection. In the first route, TIPS protection is required to install the 3-methyl and 4-iodo groups, whereas Boc is superior to Ts (and TIPS cannot be used) for subsequent Pd-mediated carbonylation with methyl potassium malonate. In the second route, 3-methyl-4-acetylpyrrole is employed with Boc protection for Claisen condensation with methyl chloroformate. Gram-scale quantities of the desired ring C pyrrole are now readily available. Studies to construct ring A, set the stereochemically defined substituents in rings B and D, and combine the four building blocks at reasonable scale form the next focus of attention.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR and ^{13}C NMR spectra were collected at room temperature in $CDCl_3$ unless noted otherwise. Electrospray ionization mass spectrometry data are reported for the molecular ion or protonated molecular ion. Anhydrous THF used in all reactions was freshly distilled from Na/benzophenone ketyl unless noted otherwise. THF (ACS-grade) and all commercially available compounds were used as received. Known compounds **TIPS-1**,[16] **TIPS-1-Br**,[17] **TIPS-1-I**,[19] **TIPS-pyrrole-Br_2**,[18] **3**,[20] **4**,[20] and **Boc-4**[25] were prepared following the literature but with refined conditions, larger scale, and/or full characterization as described here.

3-Methyl-1-(triisopropylsilyl)pyrrole (TIPS-1). Following a reported procedure[16] with streamlined implementation, a solution of **TIPS-pyrrole** (14.5 g, 65.0 mmol) in anhydrous THF (150 mL) was treated slowly with NBS (11.5 g, 65.0 mmol) at −78 °C under argon. The reaction mixture was stirred for 2 h at −78 °C, and the TLC analysis indicated that the reaction was completed. Saturated aqueous $NaHCO_3$ (150 mL) was added into the above mixture, and the reaction mixture was extracted with diethyl ether (100 mL × 3). The organic layer was dried (Na_2SO_4) and concentrated to give 3-bromo-1-(triisopropylsilyl)pyrrole as a pale yellow oil (18.9 g, 96%) that was sufficiently pure to be used in the next step. ^{1}H NMR (300 MHz): δ 1.09 (d, J = 7.5 Hz, 18H), 1.41 (q, J = 7.4 Hz, 3H), 6.29 (dd, J_1 = 2.9 Hz, J_2 = 1.4 Hz, 1H), 6.68 (d, J = 2.6 Hz, 1H), 6.71−6.75 (m, 1H). ^{13}C NMR (75 MHz): δ 11.5, 17.7, 97.9, 113.0, 123.3, 124.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{25}BrNSi$, 302.0934; found, 302.0932. A solution of the 3-bromo-1-(triisopropylsilyl)-pyrrole (18.9 g, 62.5 mmol) in anhydrous THF (250 mL) was treated dropwise with *n*-BuLi (30.0 mL, 2.5 M in hexanes, 75 mmol) at −78 °C under argon. The reaction mixture was stirred for 30 min at −78 °C. Then, the reaction mixture was treated with MeI (5.84 mL, 93.7 mmol) at −78 °C under argon. The resulting mixture was stirred for 20 min at −78 °C and then was allowed to warm to room temperature. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (200 mL), extracted with ethyl acetate (100 mL × 3), dried (Na_2SO_4), and concentrated to a yellow oil (14.8 g, quant.; 96% over two steps). ^{1}H NMR (300 MHz): δ 1.13 (d, J = 7.4 Hz, 18H), 1.38−1.50 (m, 3H), 2.16 (s, 3H), 6.17 (d, J = 1.7 Hz, 1H), 6.56 (d, J = 1.1 Hz, 1H), 6.72 (t, J = 2.4 Hz, 1H). ^{13}C NMR (75 MHz): δ 11.7, 11.9, 17.9, 111.8, 120.5, 121.7, 124.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{28}NSi$, 238.1985; found, 238.1983.

3,4-Dibromo-1-(triisopropylsilyl)pyrrole (TIPS-pyrrole-Br_2). Following a reported procedure[18] with modifications for 4-fold larger scale, a solution of **TIPS-pyrrole** (10.0 g, 45.0 mmol) in anhydrous THF (140 mL) was treated slowly with NBS (16.0 g, 90.0 mmol) at −78 °C under argon. The reaction mixture was stirred at −78 °C for 30 min and then was allowed to reach room temperature over 1 h. The reaction mixture was treated with saturated aqueous $NaHCO_3$ (90 mL), causing formation of a white precipitate. The suspension was washed with diethyl ether and filtered. The filtrate was washed with brine, dried (Na_2SO_4), and concentrated. The resulting residue was dried under high vacuum to afford a white solid. The white solid was dissolved in pentane (∼50 mL) and recrystallized at 0 °C to afford a white solid (8.75 g, 51%). mp 76−80 °C. ^{1}H NMR (400 MHz): δ 1.09 (d, J = 7.4 Hz, 18H), 1.41 (m, 3H), 6.73 (s, 2H). ^{13}C NMR (100 MHz): δ 11.4, 17.6, 101.0, 123.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{24}Br_2NSi$, 380.0039; found, 380.0036.

4-Bromo-3-methyl-1-(triisopropylsilyl)pyrrole (TIPS-1-Br). Following a reported procedure[17] with modification and 14-fold larger scale, a solution of **TIPS-pyrrole-Br_2** (7.05 g, 18.5 mmol) in anhydrous THF (85 mL) was treated dropwise with *n*-BuLi (8.14 mL, 2.5 M in hexanes, 20. mmol) at −78 °C under argon. The reaction mixture was stirred for 30 min at −78 °C and then was treated with MeI (2.30 mL, 37.0 mmol). The resulting mixture was stirred for 20 min at −78 °C and then was allowed to warm to room temperature over 1 h. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (100 mL) and then extracted with diethyl ether (50 mL × 3). The organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed [silica, hexanes] to afford a white solid (3.06 g, 48%). mp 59−62 °C. ^{1}H NMR (300 MHz): δ 1.08 (d, J = 7.4 Hz, 18H), 1.39 (m, 3H), 2.04 (s, 3H), 6.49 (d, J = 1.5 Hz, 1H), 6.68 (d, J = 2.5 Hz, 1H). ^{13}C NMR (100 MHz): δ 10.9, 11.5, 17.8, 100.8, 120.4, 121.5, 123.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{27}BrNSi$, 316.1091; found, 316.1091.

4-(3-Methoxy-1,3-dioxopropyl)-3-methyl-1-(triisopropylsilyl)pyrrole (TIPS-2). *From TIPS-1.* A suspension of dry $AlCl_3$ (1.69 g, 12.7 mmol, dried at 100 °C under high vacuum for 1 h) in anhydrous CH_2Cl_2 (22 mL) was treated with methyl malonyl

DOI: 10.1021/acs.joc.9b01650
J. Org. Chem. 2019, 84, 11286−11293

chloride (874 μL, 7.90 mmol). The mixture was stirred for 30 min at room temperature under argon. Then, a solution of **TIPS-1** (500. mg, 2.11 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise. The reaction mixture was stirred for 3 h at room temperature and then poured into an ice−water bath and acidified by the addition of 2 M HCl (5 mL). The mixture was extracted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated to a yellow liquid. The latter was chromatographed [silica, hexanes/ethyl acetate (3:2)] to afford a yellow oil (14 mg, 2.0%). ^{1}H NMR (300 MHz): δ 1.10 (d, J = 7.4 Hz, 18 H), 1.40−1.50 (m, 3H), 2.29 (s, 3H), 3.72 (s, 3H), 3.78 (s, 2H), 6.46−6.50 (m, 1H), 7.33 (d, J = 2.2 Hz, 1H). ^{13}C NMR (75 MHz): δ 11.4, 12.2, 17.6, 47.5, 52.3, 123.0, 124.3, 125.4, 132.1, 168.7, 187.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{32}NO_3Si$, 338.2146; found, 338.2146.

From ***TIPS-1-Br***. A solution of **TIPS-1-Br** (520. mg, 1.65 mmol) in anhydrous THF (8.0 mL) was treated with *n*-BuLi (793 μL, 2.5 M in hexanes, 2.0 mmol, 1.2 equiv) at −78 °C under argon. After stirring for 30 min, methyl malonyl chloride (352 μL, 3.18 mmol) was added. The reaction mixture was stirred for 20 min at −78 °C under argon and then allowed to warm to room temperature over 40 min. Saturated aqueous NH_4Cl was added. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated to a yellow oil, which was then chromatographed [silica, hexanes/ethyl acetate (2:1)] to afford a yellow oil (35 mg, 6.3%). The product gave a ^{1}H NMR spectrum identical with that above.

3-Iodo-4-methyl-1-(triisopropylsilyl)pyrrole (TIPS-1-I). (See ref 19.) Following an alternative procedure[27] with some modification, a solution of **TIPS-1** (2.42 g, 10.2 mmol) in anhydrous DMF (52 mL) was treated with NIS (2.30 g, 10.2 mmol) in batches at 0 °C under argon. After 1 h, the mixture was poured into a beaker containing a mixture of ethyl acetate (150 mL) and water (250 mL). The organic extract was washed with brine, dried (Na_2SO_4), and concentrated to a yellow liquid, which was chromatographed (silica, hexanes, 4 cm × 15 cm, first fraction, R_f = 0.50 in hexanes) to afford a white solid (2.08 g, 56%). mp 47−52 °C. ^{1}H NMR (300 MHz): δ 1.08 (d, J = 7.4 Hz, 18H), 1.34−1.46 (m, 3H), 2.03 (s, 3H), 6.51 (s, 1H), 6.75 (s, 1H). ^{13}C NMR (75 MHz): δ 11.6, 13.1, 17.8, 68.8, 121.5, 123.5, 128.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{27}INSi$, 364.0952; found, 364.0956.

4-Bromo-3-methyl-1-*p*-tosylpyrrole (Ts-1-Br). A solution of **TIPS-1-Br** (2.40 g, 7.62 mmol) in anhydrous THF (28 mL) was treated with TBAF (11.76 mL, 1 M in THF) under argon. The starting material was consumed after 10 min as determined by TLC. The reaction mixture was extracted with ethyl ether, washed with water and brine, dried (Na_2SO_4), and concentrated to a yellow liquid. *Note: the unprotected 4-bromo-3-methylpyrrole is unstable and readily decomposes, as expected for electron-rich halopyrroles.*[28] The crude 4-bromo-3-methylpyrrole was immediately dissolved in anhydrous THF (33 mL) and treated with NaH (612 mg, 15 mmol, 60% dispersion in mineral oil) at 0 °C under argon. The mixture was stirred for 10 min, and then, *p*-toluenesulfonyl chloride (2.89 g, 15.2 mmol) was added. The resulting mixture was stirred for 1.5 h at 0 °C and allowed to warm to room temperature over 30 min. The mixture was extracted with ethyl acetate, washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed [silica, hexanes/ethyl acetate (4:1)] to afford a brown mixture, which was concentrated. The resulting product was dissolved in ethyl acetate, and hexanes was added. The resulting white solid was recrystallized (ethyl acetate/hexanes) at room temperature over 2 days. The mother liquor was concentrated and dissolved in CH_2Cl_2, and then, excess hexanes was added. Recrystallization (CH_2Cl_2/hexanes) of the former white solid and material from the former mother liquor at −20 °C afforded a white solid (970 mg, 41%). mp 101 °C. ^{1}H NMR (300 MHz): δ 1.95 (s, 3H), 2.40 (s, 3H), 6.89 (s, 1H), 7.12 (s, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H). ^{13}C NMR (75 MHz): δ 10.9, 21.6, 105.7, 117.7, 119.5, 124.3, 126.9, 130.1, 135.6, 145.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{13}BrNO_2S$, 313.9845; found, 313.9846. A crystal for X-ray structure determination was obtained from hexanes/ethyl acetate.

4-Iodo-3-methyl-1-*p*-tosylpyrrole (Ts-1-I). A solution of **TIPS-1-I** (500. mg, 1.38 mmol) in anhydrous THF (5 mL) was treated with TBAF (1.66 mL, 1 M in THF) under argon. After 10 min, a mixture of ethyl acetate and hexanes (20 mL, 3:1, v/v) was added. The organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated. *Note: the unprotected 4-iodo-3-methylpyrrole is unstable and readily decomposes, as expected for electron-rich halopyrroles.*[28] The crude 4-iodo-3-methylpyrrole was immediately dissolved in anhydrous THF (10 mL) and treated with NaH (66.2 mg, 2.62 mmol, 95%). The mixture was stirred for 5 min at 0 °C and then treated with *p*-toluenesulfonyl chloride (526 mg, 2.76 mmol) under argon. The reaction mixture was stirred for 2 h at 0 °C and then 30 min at room temperature. The mixture was diluted with ethyl ether, washed with water and brine, dried (Na_2SO_4), and concentrated. The resulting residue was dissolved in CH_2Cl_2, treated with excess hexanes, and stored overnight at −20 °C. The resulting white precipitate was collected and found by TLC analysis to have a slight impurity. Chromatography [silica, CH_2Cl_2/hexanes (1:6)] afforded a white solid (230 mg, 46%). mp 99 °C. ^{1}H NMR (300 MHz): δ 1.91 (s, 3H), 2.36 (s, 3H), 6.90 (dd, J_3 = 2.4 Hz, J_2 = 1.2 Hz, 1H), 7.22 (d, J = 2.5 Hz, 1H), 7.26 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 8.1 Hz, 2H). ^{13}C NMR (75 MHz): δ 13.3, 21.7, 74.3, 117.5, 124.5, 127.0, 127.0, 130.1, 135.6, 145.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{13}INO_2S$, 361.9706; found, 361.9704. A crystal for X-ray structure determination was obtained from hexanes/ethyl acetate.

4-(3-Methoxy-1,3-dioxopropyl)-3-methyl-1-*p*-tosylpyrrole (Ts-2). *From* ***Ts-1-I***. Under the general procedure described above, a mixture of **Ts-1-I** (0.10 g, 0.28 mmol), methyl potassium malonate (69 mg, 0.44 mmol), Xantphos (96 mg, 0.17 mmol), $MgCl_2$ (42 mg, 0.44 mmol), and imidazole (38 mg, 0.55 mmol) was placed in a 25 mL Schlenk flask, which was charged with argon. THF (6.0 mL) was added followed by Et_3N (61 μL, 0.44 mmol). The mixture was degassed by three freeze−pump−thaw cycles. Then, $Pd(OAc)_2$ (48 mg, 0.22 mmol) and $Co_2(CO)_8$ (74 mg, 0.22 mmol) were added. Following the reaction work up, chromatography [silica, hexanes/ethyl acetate (3:1)] afforded a brown oil (58 mg, 63%). ^{1}H NMR (600 MHz): δ 2.21 (s, 3H), 2.43 (s, 3H), 3.73 (s, 3H), 3.76 (s, 3H), 6.88 (dd, J_3 = 2.4 Hz, J_2 = 1.3 Hz, 1H), 7.35 (d, J = 8.2 Hz, 2H), 7.71 (d, J = 2.3 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H). ^{13}C NMR (150 MHz): δ 12.0, 21.7, 47.1, 52.5, 119.6, 125.3, 126.5, 126.6, 127.2, 130.3, 135.1, 146.0, 167.7, 187.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{18}NO_5S$, 336.0900; found, 336.0899.

From ***Ts-1-Br***. Following a reported procedure[3] with slight modification, a mixture of **Ts-1-Br** (0.10 g, 0.32 mmol), methyl potassium malonate (80 mg, 0.51 mmol), Xantphos (111 mg, 0.192 mmol), $MgCl_2$ (49 mg, 0.51 mmol), and imidazole (44 mg, 0.64 mmol) was placed in a 25 mL Schlenk flask, which was charged with argon. THF (7.0 mL) was added followed by Et_3N (70 μL, 0.51 mmol). The mixture was degassed by three freeze−pump−thaw cycles. Then, $Pd(OAc)_2$ (56 mg, 0.25 mmol) and $Co_2(CO)_8$ (86 mg, 0.25 mmol) were added. The flask was sealed immediately and heated at 65 °C, with reaction progress monitored by TLC analysis. When the reaction was complete (48 h), the reaction mixture was allowed to cool to room temperature. The mixture was diluted with ethyl acetate and then filtered through a Celite pad. The filtrate was washed with brine and water, dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (3:1)] to afford a pale yellow oil (26 mg, 24%). The product gave a ^{1}H NMR spectrum identical with that above.

1-*tert*-Butoxycarbonyl-4-(3-methoxy-1,3-dioxopropyl)-3-methylpyrrole (Boc-2). *From* ***TIPS-1-I***. A solution of **TIPS-1-I** (500. mg, 1.38 mmol) in anhydrous THF (5 mL) was treated with TBAF (1.66 mL, 1 M in THF) under argon. After 10 min, ethyl ether was added, and the organic extract was washed with water and brine, dried (Na_2SO_4), and concentrated to a yellow oil. The oil was dissolved in anhydrous acetonitrile (12 mL) and treated with $(Boc)_2O$ (904 mg, 4.14 mmol) and DMAP (17 mg, 0.14 mmol). The reaction mixture was stirred for 16 h at room temperature. Removal of the solvent afforded a residue, which was filtered through a short silica pad (1% ethyl acetate in hexanes). The crude oil was

DOI: 10.1021/acs.joc.9b01650
J. Org. Chem. 2019, 84, 11286−11293

concentrated. The concentrated crude oil, methyl potassium malonate (432 mg, 2.77 mmol), Xantphos (600. mg, 1.04 mmol), $MgCl_2$ (264 mg, 2.77 mmol), and imidazole (236 mg, 3.46 mmol) were placed in a Schlenk flask, which was charged with argon. THF (37 mL) was added followed by Et_3N (373 μL, 2.72 mmol). The mixture was degassed by three freeze−pump−thaw cycles. Then, $Pd(OAc)_2$ (202 mg, 0.900 mmol) and $Co_2(CO)_8$ (308 mg, 0.901 mmol) were added. The flask was sealed immediately and heated at 65 °C for 2 days, and then, the reaction mixture was allowed to cool to room temperature. The mixture was diluted with ethyl acetate and then filtered through a Celite pad. The filtrate was washed with brine and water, dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (5:1), 3 cm × 12 cm, second fraction, R_f = 0.57 in hexanes/ethyl acetate (3:1)] to afford a yellow oil (268 mg, 69%). ^{1}H NMR (600 MHz): δ 1.61 (s, 9H), 2.25 (s, 3H), 3.75 (s, 3H), 3.79 (s, 2H), 6.97−6.99 (m, 1H), 7.79 (d, J = 2.2 Hz, 1H). ^{13}C NMR (150 MHz): δ 12.0, 27.9, 46.9, 52.4, 85.1, 119.5, 123.4, 125.7, 126.4, 147.9, 168.0, 188.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{20}NO_5$, 282.1336; found, 282.1331.

From ***Boc-4***. A stirred solution of **Boc-4** (21.65 g, 96.97 mmol) in anhydrous THF (400 mL) was cooled to −78 °C under argon and then treated with LDA (2 M solution in Et_2O, 72.5 mL). The resulting mixture was stirred at −78 °C for 15 min, followed by dropwise addition of methyl chloroformate (11.2 mL, 145 mmol) through a cannula. The reaction mixture was allowed to warm to room temperature followed by stirring for 3 h. Then, saturated aqueous NH_4Cl (500 mL) was added, and the ether layer was collected. Further extraction of residual organic matter from the aqueous layer was performed with CH_2Cl_2 (4 × 200 mL). The combined organic solution was dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (5:1)] to yield a yellow oil (10.58 g, 39%) with identical full characterization data as above.

From ***Boc-3***. Following a reported procedure[29] with modification, a sample of TMSCl (25 μL, 0.20 mmol) was added to a stirred suspension of Zn (131 mg, 2.00 mmol) in THF (1 mL), and the resulting mixture was stirred at reflux for 30 min. The mixture was then allowed to cool to room temperature followed by the addition of a small portion of methyl 2-bromoacetate (19 μL, 0.20 mmol). When the mixture turned green, samples of **Boc-3** (106 mg, 0.514 mmol) and methyl 2-bromoacetate (170 μL, 1.80 mmol) were slowly added in simultaneous fashion to the reaction mixture over the course of 60 min. The resulting mixture was then brought to reflux for 4 h, and then allowed to cool to room temperature followed by the addition of 3 N HCl (1 mL). After stirring at room temperature for 30 min, the reaction mixture was treated with aqueous 50% K_2CO_3 until basic and then extracted with ethyl acetate (3 × 5 mL). The combined organic extract was dried (Na_2SO_4) and concentrated to give a crude brown oil. ^{1}H NMR analysis in the presence of 1,1,2,2-tetrachloroethane as an internal standard indicated that the desired **Boc-2** was formed in 3% yield.

4-(3-Methoxy-1,3-dioxopropyl)-3-methylpyrrole (2). *From* ***Boc-2***. Compound **Boc-2** (10.58 g, 37.61 mmol) was added to a solution of 25% TFA in CH_2Cl_2 (160 mL). The resulting reaction mixture was stirred at room temperature for 4 h, after which TLC analysis [silica, hexanes/ethyl acetate (1:1)] indicated completion of the reaction. Saturated aqueous $NaHCO_3$ (750 mL) was slowly added, and the resulting mixture was extracted with CH_2Cl_2 (4 × 200 mL). The combined organic extract was washed with water and brine, dried (Na_2SO_4), and concentrated to give a brown oil (6.16 g, 90%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.30 (s, 3H), 3.73 (s, 3H), 3.78 (s, 2H), 6.56 (s, 1H), 7.39 (s, 1H), 8.67 (br, 1H). ^{13}C (125 MHz, $CDCl_3$): δ 12.1, 47.2, 52.3, 118.5, 121.4, 123.1, 125.7, 168.7, 187.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_9H_{12}NO_3$, 182.0812; found, 182.0817.

From ***TIPS-2***. A solution of **TIPS-2** (10.0 mg, 29.7 μmol) in anhydrous THF (0.5 mL) was treated with TBAF (89.1 μL, 1 M in THF). The reaction mixture was stirred for 30 min at room temperature before adding a mixture of ethyl ether and saturated aqueous NH_4Cl. The organic extract was washed with brine, dried, and concentrated. The residue was passed through a glass pipet column [silica, hexanes/ethyl acetate (1:2)] to afford a transparent oil (5.0 mg, 93%). The product gave a ^{1}H NMR spectrum identical with that above

From ***Ts-2***. A solution of **Ts-2** (12.0 mg, 35.8 μmol) in anhydrous THF (1.0 mL) was treated with TBAF (150 μL, 1 M in THF) at 65 °C. The reaction progress was monitored by TLC. After 6 h, another 150 μL of TBAF (1 M in THF) was added, and the mixture was stirred for 18 h. Then, the flask was allowed to cool to room temperature, whereupon a mixture of ethyl acetate and water was added. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed [silica, hexanes/ethyl acetate] to afford a transparent oil (1.3 mg, 20%). The product gave a ^{1}H NMR spectrum identical with that above.

2-Iodo-4-(3-methoxyl-1,3-diooxopropyl)-3-methylpyrrole (2-I). Following a general procedure,[3] a solution of **2** (6.16 g, 34.0 mmol) in anhydrous DMF (450 mL) was stirred at 0 °C, followed by the slow addition of NIS (7.65 g, 34.0 mmol) in portions over 5 min. The resulting solution was stirred at 0 °C for 1 h and then diluted with water (500 mL) and ethyl acetate (500 mL). The organic layer was collected, and the aqueous layer was further extracted with ethyl acetate (3 × 200 mL). The combined organic extract was washed with water and brine, dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (1:1)] to afford a light-yellow solid (7.92 g, 76%). mp 123−125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.27 (s, 3H), 3.74 (s, 3H), 3.76 (s, 2H), 7.51 (d, J = 2.7 Hz, 1H), 8.30 (br, 1H). ^{13}C (125 MHz, $CDCl_3$): 13.7, 46.8, 52.5, 124.0, 126.9, 128.7, 168.4, 186.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_9H_{11}INO_3$, 307.9778; found, 307.9785.

4-Cyano-3-methylpyrrole (3). Following a reported procedure[20] with modification, 4-fold larger scale, and more complete characterization, NaH (60% dispersion in mineral oil, 3.34 g, 84 mmol) was placed in a 1000 mL flask and washed several times with hexanes. The resulting suspension of NaH in hexanes (approximately 20 mL) was then diluted with Et_2O (140 mL). A solution of TosMIC (14.06 g, 72.01 mmol) and crotononitrile (*E* and *Z* mixture, 3.35 g, 50.0 mmol) in DMSO (110 mL) and Et_2O (220 mL) was added slowly to the suspension of NaH with vigorous stirring. After the addition, the reaction mixture was stirred at room temperature for 1.5 h. The resulting mixture was diluted with water (200 mL) and extracted with Et_2O (4 × 100 mL). The combined ethereal extract was washed with water and brine, dried (Na_2SO_4), concentrated, and subjected to short column chromatography [silica, hexanes/ethyl acetate (3:1)] to afford a yellow solid (4.44 g, 84%). mp 40−42 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 2.19 (s, 3H), 6.57 (s, 1H), 7.21 (s, 1H), 8.69 (br, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.4, 94.3, 116.68, 116.73, 122.3, 125.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_6H_7N_2$, 107.0604; found, 107.0602.

1-*tert*-Butyloxycarbonyl-4-cyano-3-methylpyrrole (Boc-3). Following a general procedure,[26] samples of $(Boc)_2O$ (11.46 g, 52.51 mmol), Et_3N (7.23 mL, 52.5 mmol), and DMAP (214 mg, 1.75 mmol) were added to a stirred solution of **3** (3.71 g, 35.0 mmol) in CH_2Cl_2 (150 mL). A brisk and instantaneous evolution of gas was observed. The resulting reaction mixture was stirred at room temperature for 20 min, after which TLC analysis [silica, hexanes/ethyl acetate (3:1)] indicated complete consumption of starting material. The resulting reaction mixture was concentrated and chromatographed on a short column [silica, hexanes/ethyl acetate (3:1)] to give a yellow oil (5.98 g, 83%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.60 (s, 9H), 2.16 (s, 3H), 7.01 (s, 1H), 7.63 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.4, 27.9, 85.5, 98.9, 114.8, 118.2, 123.8, 126.9, 147.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{11}H_{15}N_2O_2$, 207.1128; found, 207.1126. Alternatively, NaH (60% dispersion in mineral oil, 5.00 g, 125 mmol) was placed in a 1000 mL flask and washed several times with hexanes. The resulting suspension of NaH in hexanes (approximately 30 mL) was then diluted with Et_2O (150 mL). A solution of TosMIC (21.00 g, 107.5 mmol) and crotononitrile (*E* and *Z* mixture, 5.55 g, 82.7 mmol) in DMSO (120 mL) and Et_2O (250 mL) was added slowly with vigorous stirring of the NaH suspension. After the addition, the reaction mixture was

DOI: 10.1021/acs.joc.9b01650
J. Org. Chem. 2019, 84, 11286−11293

stirred at room temperature for 2 h. Then, $(Boc)_2O$ (20.70 g, 94.85 mmol) was added, and a brisk and instantaneous evolution of gas was observed. The resulting mixture was stirred at room temperature for 1 h before being treated with saturated aqueous NH_4Cl (400 mL) followed by extraction with Et_2O (4 × 150 mL). The combined organic extract was washed with water and brine, dried (Na_2SO_4), concentrated, and subjected to short column chromatography [silica, hexanes/ethyl acetate (3:1)] to give a yellow oil (12.53 g, 73%) with the same ^1H NMR and HRMS data as reported above.

4-Acetyl-3-methylpyrrole (4). Following a general procedure[20] with modification, 14-fold larger scale, and more complete characterization, NaH (60% dispersion in mineral oil, 1.68 g, 42 mmol) was placed in a 500 mL flask and washed several times with hexanes. The suspension of NaH in hexanes (approximately 10 mL) was then diluted with Et_2O (70 mL). A solution of TosMIC (7.03 g, 36.0 mmol) and 4-oxo-2-pentene (*E* and *Z* mixture, 85% purity, 2.47 g, 25.0 mmol) in DMSO (55 mL) and Et_2O (110 mL) was added slowly to the suspension of NaH with vigorous stirring. After the addition, the reaction mixture was stirred at room temperature for further 1 h. The resulting mixture was diluted with water (150 mL) and extracted with Et_2O (3 × 150 mL). The combined ethereal extract was washed with water and brine, dried (Na_2SO_4), concentrated, and subjected to short column chromatography [silica, hexanes/ethyl acetate (2:1)] to afford a yellow solid (2.80 g, 91%). mp 113−115 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 2.32 (s, 3H), 2.40 (s, 3H), 6.55 (s, 1H), 7.35 (s, 1H), 8.53 (br, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.2, 27.9, 118.0, 120.8, 124.3, 124.9, 194.4. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_7H_{10}NO$, 124.0757; found, 124.0759.

4-Acetyl-3-methyl-1-(triisopropylsilyl)pyrrole (TIPS-4). Following a general procedure,[24] a solution of **4** (1.96 g, 15.9 mmol) in anhydrous DMF (4 mL) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 764 mg, 19 mmol) in anhydrous DMF (24 mL) at 0 °C. Stirring was continued for 1 h, followed by dropwise treatment with TIPS-Cl (4.09 mL, 19.1 mmol) and further stirring at 0 °C for 45 min. The reaction mixture was then diluted with water (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic extract was washed with water and brine, dried (Na_2SO_4), concentrated, and chromatographed on a short column [silica, hexanes/ethyl acetate (5:1)] to yield a white solid (3.91 g, 88%). mp 58−60 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 1.11 (d, J = 7.6 Hz, 18 H), 1.45 (hept, J = 7.5 Hz, 3H), 2.30 (s, 3H), 2.40 (s, 3H), 6.48 (s, 1H), 7.30 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.5, 12.4, 17.7, 27.9, 122.3, 124.1, 126.6, 131.4, 194.4. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{30}NOSi$, 280.2091; found, 280.2088.

1-*tert*-Butoxycarbonyl-4-acetyl-3-methylpyrrole (Boc-4). (See ref 25.) Following a new procedure,[26] samples of $(Boc)_2O$ (10.80 g, 49.48 mmol), Et_3N (6.90 mL, 49.5 mmol), and DMAP (1.00 g, 8.25 mmol) were added to a stirred solution of **4** (4.06 g, 33.0 mmol) in CH_2Cl_2 (150 mL). A brisk and instantaneous evolution of gas was observed. The resulting reaction mixture was stirred at room temperature for 1 h, after which TLC analysis [silica, hexanes/ethyl acetate (2:1)] indicated complete consumption of **4**. The resulting reaction mixture was concentrated and then chromatographed on a short column [silica, hexanes/ethyl acetate (2:1)] to give a yellow oil (6.35 g, 85%). ^1H NMR (500 MHz, $CDCl_3$): δ 1.61 (s, 9H), 2.25 (s, 3H), 2.41 (s, 3H), 6.96 (s, 1H), 7.76 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.1, 27.8, 27.9, 84.8, 119.2, 123.1, 126.0, 126.7, 148.2, 194.5. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{18}NO_3$, 224.1281; found, 224.1285. For an alternative one-flask procedure, a sample of NaH (60% dispersion in mineral oil, 4.80 g, 120 mmol) in a 1000 mL flask was washed several times with hexanes. The resulting suspension of NaH in hexanes (approximately 30 mL) was then diluted with Et_2O (150 mL). A solution of TosMIC (20.30 g, 103.9 mmol) and 4-oxo-2-pentene (*E* and *Z* mixture, 70% purity, 10.00 g, 83.21 mmol) in DMSO (120 mL) and Et_2O (240 mL) was added slowly to the suspension of NaH with vigorous stirring. After the addition, the reaction mixture was stirred at room temperature for 2 h. Then, $(Boc)_2O$ (18.16 g, 83.21 mmol), Et_3N (8.60 mL, 61.7 mmol), and DMAP (507 mg, 4.15 mmol) were added whereupon a brisk and instantaneous evolution of gas was observed. The resulting mixture was stirred at room temperature for 2 h before being treated with saturated aqueous NH_4Cl (400 mL) followed by extraction with Et_2O (5 × 100 mL). The combined organic extract was washed with water and brine, dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (5:1)] to give a yellow oil (11.55 g, 62%) with the same ^1H NMR spectrum as reported above.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b01650.

^1H and ^{13}C NMR spectra for all compounds (PDF)

X-ray data for **Ts-1-Br** (CIF)

X-ray data for **Ts-1-I** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jlindsey@ncsu.edu. Phone: 919-515-6406.

ORCID

Pengzhi Wang: 0000-0003-4813-6639

Khiem Chau Nguyen: 0000-0002-6968-6405

Jonathan S. Lindsey: 0000-0002-4872-2040

Author Contributions

†P.W. and K.C.N. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the NSF (CHE-1760839). Mass spectrometry measurements were carried out in the Molecular Education, Technology, and Research Innovation Center (METRIC) at NC State University.

■ REFERENCES

(1) Liu, Y.; Zhang, S.; Lindsey, J. S. Total Synthesis Campaigns Toward Chlorophylls and Related Natural Hydroporphyrins − Diverse Macrocycles, Unrealized Opportunities. *Nat. Prod. Rep.* **2018**, *35*, 879−901.

(2) Scheer, H. An Overview of Chlorophylls and Bacteriochlorophylls: Biochemistry, Biophysics, Functions and Applications. In *Chlorophylls and Bacteriochlorophylls. Biochemistry, Biophysics, Functions and Applications*; Grimm, B., Porra, R. J., Rüdiger, W., Scheer, H., Eds.; Springer: Dordrecht, The Netherlands, 2006; Vol. *25*, pp 1−26.

(3) Zhang, S.; Lindsey, J. S. Construction of the Bacteriochlorin Macrocycle with Concomitant Nazarov Cyclization To Form the Annulated Isocyclic Ring: Analogues of Bacteriochlorophyll *a*. *J. Org. Chem.* **2017**, *82*, 2489−2504.

(4) Lindsey, J. S. *De Novo* Synthesis of Gem-Dialkyl Chlorophyll Analogues for Probing and Emulating our Green World. *Chem. Rev.* **2015**, *115*, 6534−6620.

(5) Malona, J. A.; Colbourne, J. M.; Frontier, A. J. A General Method for the Catalytic Nazarov Cyclization of Heteroaromatic Compounds. *Org. Lett.* **2006**, *8*, 5661−5664.

(6) Malona, J. A. Scandium (III) Catalyzed Nazarov Cyclization of Heteroaryl-Vinyl Ketones. II. Efforts Towards the Total Synthesis of (±) - Rocaglamide *via* a Nazarov Cyclization Strategy. III. Efforts Towards the Total Synthesis of (±) - Rocaglamide *via* an Alkoxy Allene Epoxidation/Nazarov Cyclization. Ph.D. Dissertation, University of Rochester, Rochester, NY, 2008.

(7) Fujiwara, M.; Kawatsura, M.; Hayase, S.; Nanjo, M.; Itoh, T. Iron(III) Salt-Catalyzed Nazarov Cyclization/Michael Addition of Pyrrole Derivatives. *Adv. Synth. Catal.* **2009**, *351*, 123−128.

DOI: 10.1021/acs.joc.9b01650
J. Org. Chem. 2019, 84, 11286−11293

(8) Howarth, T. T.; Jackson, A. H.; Judge, J.; Kenner, G. W.; Newman, D. J. Pyrroles and Related Compounds. Part XXVI. Pyrrole β-Keto-esters. *J. Chem. Soc., Perkin Trans. 1* **1974**, *1*, 490−501.
(9) Bamaung, N. Y.; Djuric, S. W.; Gubbins, E. J.; Luly, J. R.; Tu, N. P.; Madar, D. J.; Warrior, U.; Wiedeman, P. E.; Zhou, X.; Sciotti, R. J.; Wagenaar, F. L. Azole Inhibitors of Cytokine Production. U.S. Patent Appl. 2001/0044445 A1, 2001.
(10) Wahl, B.; Basha, A.; Bonin, H.; Mortreux, A.; Giboulot, S.; Liron, F.; Poli, G.; Sauthier, M. A General and Efficient Method for the Alkoxycarbonylation of α-Chloro Ketones. *Adv. Synth. Catal.* **2012**, *354*, 3105−3114.
(11) Zhestkov, V. P.; Mironov, A. F.; Evstigneeva, R. P. Synthesis of Higher Alkyl Pyrrolyl Ketones. *J. Gen. Chem. USSR* **1975**, *45*, 690.
(12) Zhestkov, V. P.; Mironov, A. F.; Rozynov, B. V.; Ustynyuk, L. A.; Myagkova, G. I.; Evstigneeva, R. P. Investigations in the Field of Porphyrin *a*. II. Synthesis of Porphyrins Containing Higher Saturated and Unsaturated Acyl Substituents. *Sov. J. Bioorg. Chem.* **1976**, *2*, 880−884.
(13) Zhestkov, V. P.; Voronin, V. G.; Suslina, M. L.; Zaks, A. S. Synthesis and Biological Activity of Some Pyrrolyl Derivatives of Pyrazolone-5. *Pharm. Chem. J.* **1982**, *16*, 455−460.
(14) Nigst, T. A.; Westermaier, M.; Ofial, A. R.; Mayr, H. Nucleophilic Reactivities of Pyrroles. *Eur. J. Org. Chem.* **2008**, *2008*, 2369−2374.
(15) Mayr, H.; Lakhdar, S.; Maji, B.; Ofial, A. R. A Quantitative Approach to Nucleophilic Organocatalysis. *Beilstein J. Org. Chem.* **2012**, *8*, 1458−1478.
(16) Outlaw, V. K.; Townsend, C. A. A Practical Route to Substituted 7-Aminoindoles from Pyrrole-3-carboxaldehydes. *Org. Lett.* **2014**, *16*, 6334−6337.
(17) Shum, P. W.; Kozikowski, A. P. A Convenient Method for the Synthesis of Unsymmetrical 3,4-Disubstituted Pyrroles. *Tetrahedron Lett.* **1990**, *31*, 6785−6788.
(18) Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowsk, J. M. *N*-(Triisopropylsilyl)pyrrole. A Progenitor "Par Excellence" of 3-Substituted Pyrroles. *J. Org. Chem.* **1990**, *55*, 6317−6328.
(19) Chan, H.-W.; Chan, P.-C.; Liu, J.-H.; Wong, H. N. C. 3,4-Bis(trimethylsilyl)-1*H*-pyrrole: A Versatile Building Block for Unsymmetrically 3,4-Disubstituted Pyrroles. *Chem. Commun.* **1997**, 1515−1516.
(20) Knowles, J. P.; Booker-Milburn, K. I. Unusually Facile Thermal Homodienyl-[1,5]-Hydrogen Shift Reactions in Photochemically Generated Vinyl Aziridines. *Chem. - Eur. J.* **2016**, *22*, 11429−11434.
(21) Prakash Rao, H. S.; Rafi, S.; Padmavathy, K. The Blaise Reaction. *Tetrahedron* **2008**, *64*, 8037−8043.
(22) van Leusen, A. M.; Siderius, H.; Hoogenboom, B. E.; van Leusen, D. A New and Simple Synthesis of the Pyrrole Ring System from Michael Acceptors and Tosylmethylisocyanides. *Tetrahedron Lett.* **1972**, *13*, 5337−5340.
(23) Ma, Z.; Ma, Z.; Zhang, D. Synthesis of Multi-Substituted Pyrrole Derivatives Through [3 + 2] Cycloaddition with Tosylmethyl Isocyanides (TosMICs) and Electron-Deficient Compounds. *Molecules* **2018**, *23*, 2666.
(24) Conrad, J. C.; Kong, J.; Laforteza, B. N.; MacMillan, D. W. C. Enantioselective α-Arylation of Aldehydes via Organo-SOMO Catalysis. An Ortho-Selective Arylation Reaction Based on an Open-Shell Pathway. *J. Am. Chem. Soc.* **2009**, *131*, 11640−11641.
(25) Kettschau, G. Ph.D. Dissertation, Georg-August-Universität zu Göttingen, 1996; pp 134−135.
(26) Willumstad, T. P.; Haze, O.; Mak, X. Y.; Lam, T. Y.; Wang, Y.-P.; Danheiser, R. L. Batch and Flow Photochemical Benzannulations Based on the Reaction of Ynamides and Diazo Ketones. Application to the Synthesis of Polycyclic Aromatic and Heteroaromatic Compounds. *J. Org. Chem.* **2013**, *78*, 11450−11469.
(27) Liu, Y.; Lindsey, J. S. Northern−Southern Route to Synthetic Bacteriochlorins. *J. Org. Chem.* **2016**, *81*, 11882−11897.
(28) Artico, M. Nitration, Sulfonation, and Halogenation. In *Pyrroles. Part One. The Synthesis and the Physical and Chemical Aspects of the Pyrrole Ring*; Jones, A. R., Ed.; John Wiley & Sons: New York, 1990; pp 329−395.
(29) Prakash Rao, H. S.; Padmavathy, K.; Vasantham, K.; Rafi, S. Novel Synthesis of Methyl Ketones Based on the Blaise Reaction. *Synth. Commun.* **2009**, *39*, 1825−1834.

DOI: 10.1021/acs.joc.9b01650
J. Org. Chem. 2019, 84, 11286−11293