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Total Synthesis of the Marine Alkaloid Discoipyrrole C via the MoOPH-Mediated Oxidation of a 2,3,5-Trisubstituted Pyrrole

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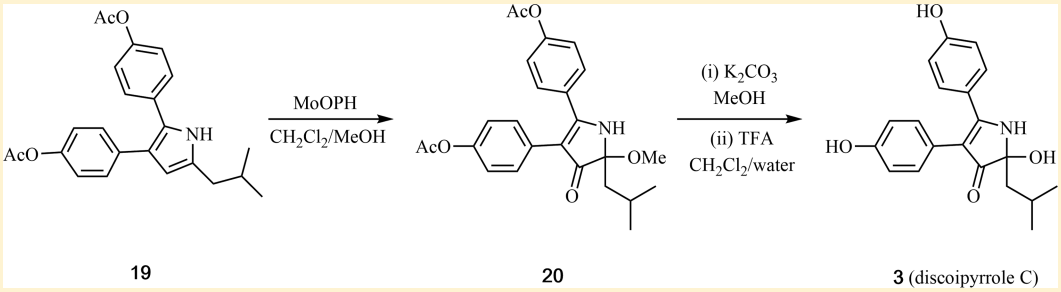
Supporting Information



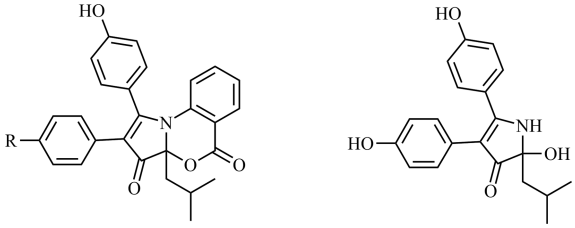
19 20 3 (discoipyrrole C)

ABSTRACT: A total synthesis of the marine alkaloid discoipyrrole C (**3**) is described. In the pivotal step, the 2,3,5-trisubstituted pyrrole **19** was treated with MoOPH in the presence of MeOH, and the resulting methoxylated 1,2-dihydro-3*H*-pyrrol-3-one **20** subjected to reaction with potassium carbonate in MeOH then trifluoroacetic acid and H_2O. This gave a mixture of target **3** and its dehydration product, and the structure of the former compound was confirmed by single-crystal X-ray analysis.

The production of discoipyrroles A−D by the marine bacterium *Bacilluus hunanensis* was reported by the MacMillan group in 2013 and, on the basis of a range of spectroscopic studies, these alkaloids were assigned structures **1**−**4**, respectively.[1] In addition to congeners **1**, **2**, and **4** embodying the previously unobserved 3*H*-benzo[*d*]pyrrole-[1,3]oxazine-3,5-dione heterocyclic framework, all four compounds showed intriguing biological properties. Specifically, each of them inhibited the discoidin domain receptor 2 or DDR2-dependent migration of BR5 fibroblasts. They also showed selective cytotoxicity toward DDR2 mutant lung cancer cell lines with IC_{50} values in the 120 to 400 nM range.[1]

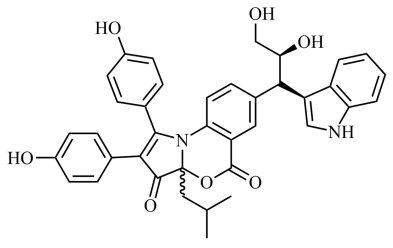
The racemic nature of the first three of these alkaloids and the isolation of the fourth as a ca. 1:1 mixture of diastereoisomers led to the proposal that the core structures of the discoipyrroles are produced in vivo by nonenzymatic pathways.[1,2] Support for this proposition followed from the in vitro assembly, under close to physiological conditions, of congener **1** from co-occurring and structurally simpler metabolites.[1,2] This biomimetic approach to the alkaloids has also been used to prepare a range of analogues including the bis-*O*-methyl ether of compound **4**.[3]

We have recently described[4,5] modular total syntheses of discoipyrroles A, B, and D that involve, as key intermediates, tetrasubstituted pyrroles wherein a benzoic acid moiety is attached to the ring-nitrogen through the *ortho*-position. On treatment of such systems with oxodiperoxymolybdenum-(pyridine)(hexamethylphosphoric triamide) (MoOPH),[6,7] they undergo oxidative cyclization with the carboxylic acid residue acting as an internal nucleophile, thus producing the central hetereocyclic ring system characteristic of compounds **1**, **2**, and **4**. While discoipyrrole C (**3**) is the structurally simplest member of this small family of natural products, it is distinct because it lacks the benzannulated 1,3-oxazinan-6-one ring system associated with congeners **1**, **2**, and **4**. Rather it embodies a 2-alkyl-2-hydroxy-1,2-dihydro-3*H*-pyrrol-3-one core and thus bears some structural resemblance to the biologically



1 (R = HO, discoipyrrole A)
2 (R = H, discoipyrrole B)

3 (discoipyrrole C)



4 (discoipyrrole D)

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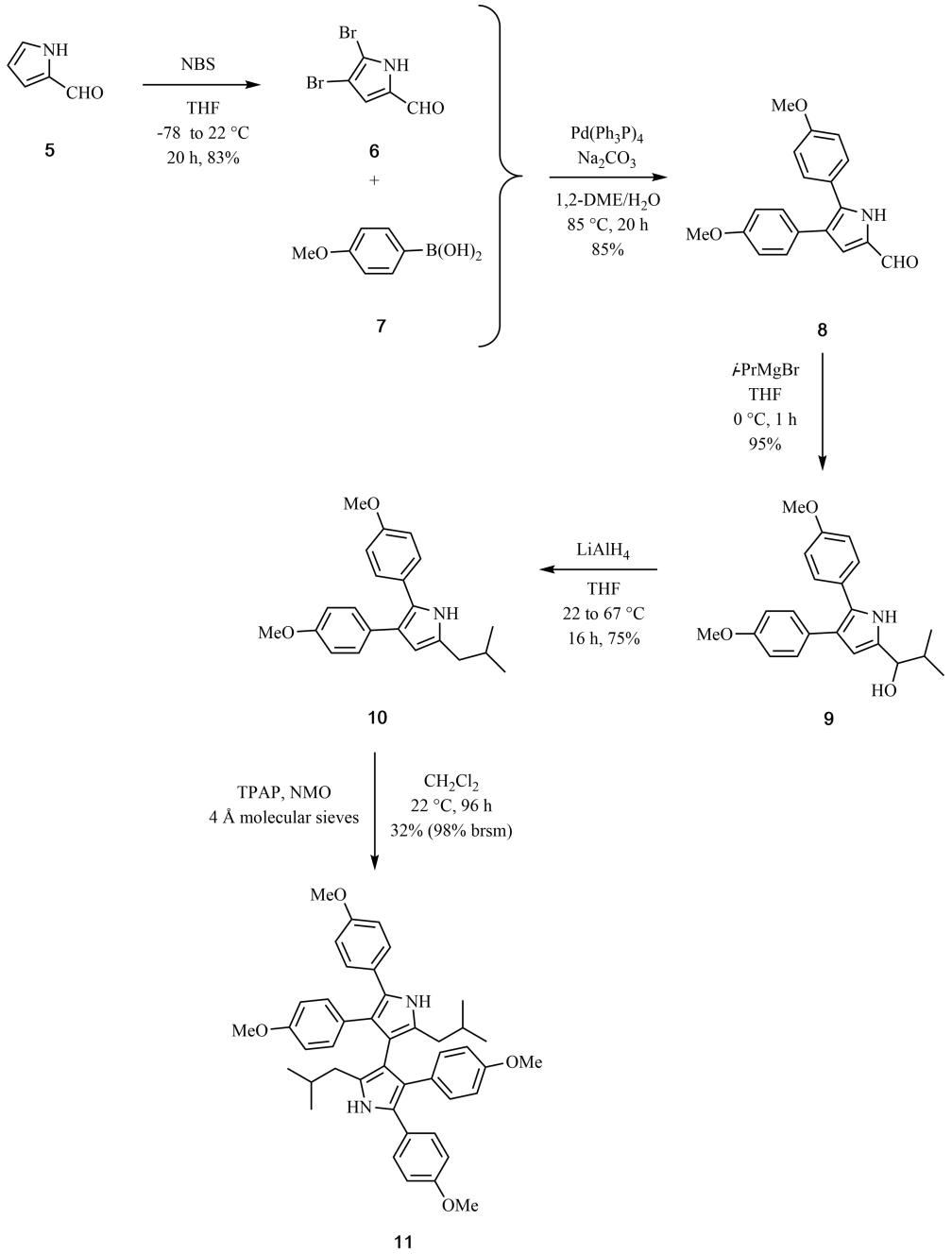
Scheme 1. Synthesis of the 2,3,5-Trisubstituted Pyrrole 10 and its Reaction with the Ley−Griffith Reagent



active natural products myceliothermophins A and B, oteromycin, pyrrocidine A, and PI-090 (each of which embodies a 5-alkyl-5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-one moiety).[8,9] The labile nature of the core of discoipyrrole C, its intriguing biological properties, and the lack of any published work on its synthesis prompted us to begin exploring methods for doing so. Herein we report the outcomes of our studies on this topic that have culminated in the total synthesis of compound **3** and its characterization by single-crystal X-ray analysis.

RESULTS AND DISCUSSION

Converting the 2,3,5-Trisubstituted Pyrrole 10 into the Corresponding 2-Alkyl-2-hydroxy-1,2-dihydro-3*H*-pyrrol-3-one. Our initial studies (Scheme 1) focused on establishing whether or not a 2,3,5-trisubstituted pyrrole (and, therefore, lacking a substituent on the ring nitrogen) could be oxidized in the presence of a nucleophilic solvent such as MeOH (and in an analogous way to that observed for certain indoles[7]) so as to generate a 2-alkyl-2-methoxy-1,2-dihydro-3*H*-pyrrol-3-one that it was expected could be hydrolyzed to form the heterocyclic core of discoipyrrole C. So, following our earlier work, the readily available pyrrole-2-carboxaldehyde (**5**) was brominated using *N*-bromosuccinimide (NBS) at low temperature, thereby generating the known[4a] dibromo-derivative **6** (83%). Compound **6** was readily engaged in a 2-fold Suzuki−Miyaura cross-coupling reaction with an excess of the commercially available arylboronic acid **7** under standard conditions, thus affording the previously reported[4a] diarylated pyrrole **8** (85%), and this was itself treated with isopropylmag-

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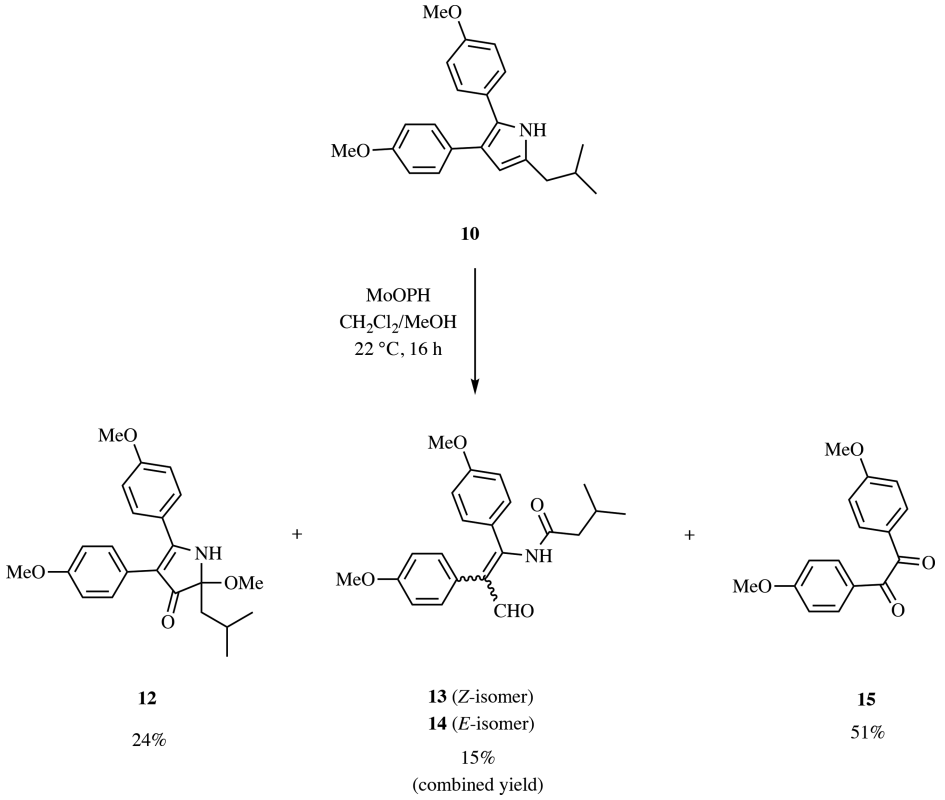
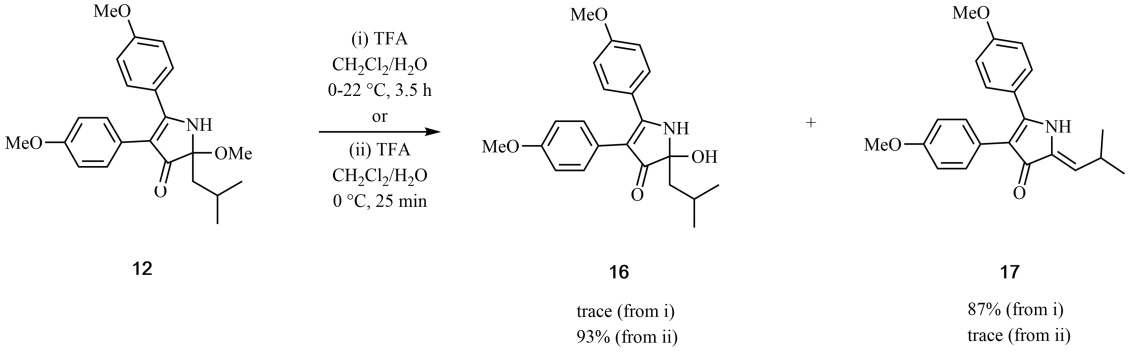
Scheme 2. Outcome of the Oxidation of Pyrrole 10 with MoOPH in the Presence of MeOH



Scheme 3. Outcomes of Treating Compound 12 with Aqueous Acid



nesium bromide to afford the secondary alcohol **9**[4a] in 95% yield. Treatment of compound **9** with lithium aluminum hydride resulted in its reductive deoxygenation to afford the required 2,3,5-trisubstituted pyrrole **10**[4a] in 75% yield. In an initial attempt to effect the desired oxidation of compound **10** it was treated with the Ley–Griffith reagent.[10,11] A very slow and clean reaction ensued, but this involved an oxidative dimerization process that afforded the bis-pyrrole **11** (98% brsm), the structure of which was determined by single-crystal X-ray analysis. No evidence for the formation of the desired 2-alkyl-2-methoxy-1,2-dihydro-3*H*-pyrrol-3-one was obtained.

In contrast to the foregoing, when a 1:1 v/v CH_2Cl_2/MeOH solution of substrate **10** was treated with MoOPH[6] at ambient temperatures, a quite distinct oxidation process (Scheme 2) took place, thus affording a mixture of compounds **12** (24%), **13** and **14** (15% combined yield), and the known[12] diketone **15** (51%). Subjection of this mixture to flash column chromatography allowed for the isolation of the first and last of these products in pure form, while amides **13** and **14** were obtained as a ca. 1:1 mixture. The spectroscopic data recorded on the 2-alkyl-2-methoxy-1,2-dihydro-3*H*-pyrrol-3-one **12** were in complete accord with the assigned structure, but final confirmation of this followed from a single-crystal X-ray analysis. On the other hand, the spectroscopic data recorded on 4,4′-dimethoxybenzil (**15**) matched those reported in the literature.[12] The mixture of compounds **13** and **14** was obtained as a crystalline conglomerate, and an individual crystal of each was subjected to X-ray analysis, thereby establishing the illustrated structures for them. Clearly compounds **13**, **14**, and **15** result from oxidative cleavage of the pyrrole ring[11] associated with the starting material **10**, but the details of the pathway(s) involved have yet to be fully investigated.

Despite the dominance of the oxidative cleavage processes described immediately above, sufficient quantities of compound **12** could be obtained so as to test whether or not it could be successfully hydrolyzed to give the corresponding 2-hydroxy-1,2-dihydro-3*H*-pyrrol-3-one. Disappointingly, on treating this

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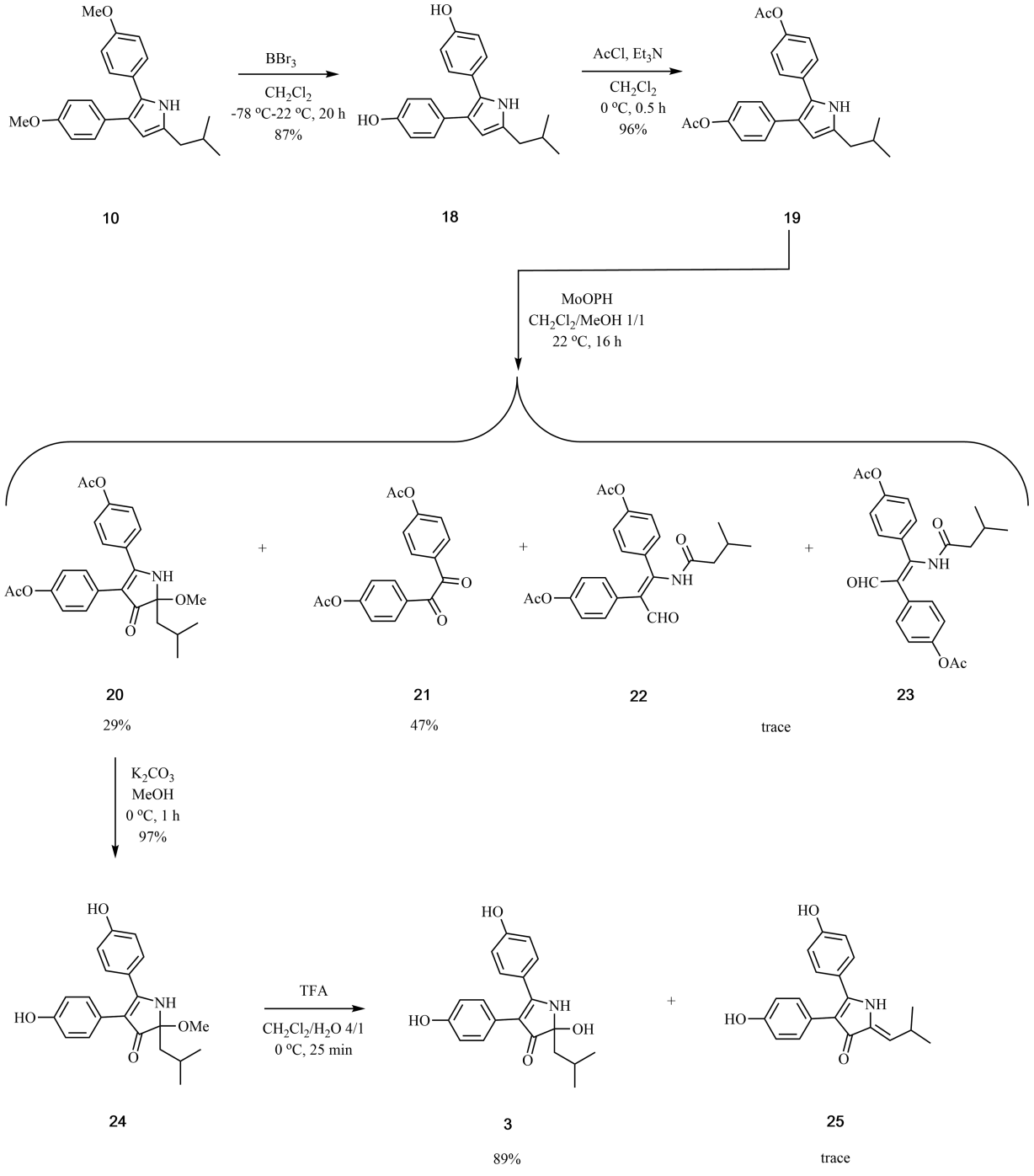
Scheme 4. Completion of a Total Synthesis of Discoipyrrole C (3)



substrate with trifluoroacetic acid (TFA) in a mixture of CH_2Cl_2 and H_2O under conditions similar to those employed by Uchiro and co-workers (Scheme 3),[8,9] only traces of the target compound **16** were observed, the major one formed being the elimination product **17** (87%) embodying an exocyclic olefin. The illustrated *Z*-configuration about this double bond is assigned by analogy with the work of Uchiro and co-workers.[8] Fortunately, when the same substrate was treated with TFA in the same solvent mixture but now at lower temperatures and for shorter periods of time, compound **16** was produced in 93% yield. All of the spectroscopic data acquired on product **16**, which represents the bis-*O*-methyl ether of discoipyrrole C, were completely in accord with the assigned structure. The strong resemblance of these data to those reported[1] for natural product **3** was notable.

Various attempts were made to convert, through 2-fold demethylation, bis-ether **16** into discoipyrrole C including by treating the former compound with boron tribromide. Unsurprisingly, though, only decomposition of the substrate was observed under such conditions.[3,5] Accordingly, a pathway to compound **3** was pursued wherein such a demethylation reaction was effected prior to the pyrrole oxidation step. The successful outcome of this approach is detailed immediately below.

Completing a Total Synthesis of Discoipyrrole C. A synthesis of discoipyrrole C (**3**) that exploited the results of the

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above-mentioned studies is outlined in Scheme 4. This started with the 2-fold demethylation of the diarylated pyrrole **10** using boron tribromide. The resulting bis-phenol **18** (87%) was acetylated under conventional conditions, and the bis-ester **19** (96%) so-formed was treated with MoOPH in CH_2Cl_2/MeOH, thus affording a mixture of compounds **20** and **21** in ca. 80% combined yield. Traces of the isomeric α-aryl-β-amidocinnamates **22** and **23** were also evident in the ^{1}H NMR spectrum of the crude reaction mixture obtained from the oxidation of pyrrole **19**, but these could not be obtained in quantities sufficient for rigorous characterization. In contrast, each of oxidation products **20** and **21**[13] could be purified by flash column chromatography and fully characterized. When compound **20** was treated with potassium carbonate in MeOH, the bis-phenol **24** was obtained in 97% yield. Exposure of compound **24** to TFA in a CH_2Cl_2/H_2O mixture at 0 °C for less than an hour followed by workup in the cold then gave discoipyrrole C (**3**) in 89% yield. Traces of the dehydration product **25** were also produced under these conditions, and more of this (61%) was formed when extended reaction times and higher temperatures were employed in the hydrolysis step (see Experimental Section). Once again, the illustrated *Z*-configuration about this double bond is assigned by analogy with the work of Uchiro and co-workers.[8]

All of the spectroscopic data acquired on the synthetically derived compounds **3** and **25** were in full accord with the illustrated structures, and those derived from the former product proved an excellent match with those reported[1] for discoipyrrole C by the MacMillan group (see the Supporting Information for a tabulated comparison of the relevant ^{13}C NMR data sets). A single-crystal X-ray analysis was undertaken on compound **3**, and this served to confirm its structure and, therefore, that of the natural product.

It is interesting to note that the heterocyclic core associated with the dehydration product **25** is similar to that seen in the natural product myceliothermophin E.[8] Furthermore, there were indications that, on standing, compound **25** began to rearrange to its *E*-isomer. A related isomerization was observed during the synthesis of myceliothermophin E.[8]

CONCLUSIONS

The MoOPH-mediated oxidation of *N*-unsubstituted pyrroles provides a hitherto unrecognized capacity to generate functionalized 1,2-dihydro-3*H*-pyrrol-3-ones such as discoipyrrole C. The opportunities to extend the types of processes reported here to related systems seem significant, although there is an attendant need to understand the mechanistic detail of these reactions and thereby optimize them. Work directed to such ends are now underway in our laboratories, and the outcomes of relevant studies will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were measured on an Optimelt automated melting point system and are uncorrected. Infrared spectra (ν_{max}) were recorded on a Perkin−Elmer 1800 Series FTIR spectrometer. Samples were analyzed as thin films on KBr plates. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$, CD_3OD, or $(CD_3)_2CO$ on a Varian spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ triplet appearing at δ_C 77.2 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. For spectra recorded in CD_3OD these were referenced to the signals at δ_H 3.31 and δ_C 49.0, respectively, while the equivalent resonances employed for spectra recorded in $(CD_3)_2CO$ were 2.05 and 29.8/206.3 ppm. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph−mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Analytical thin-layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (conc)/H_2O (37.5 g:7.5 g:37.5 g:720 mL) or potassium permanganate/potassium carbonate/5% sodium hydroxide aqueous solution/H_2O (3 g:20 g:5 mL; 300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.[14] with silica gel 60 (40−63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. The melting points of solids purified by such means were recorded directly (i.e., after they had crystallized from the concentrated chromatographic fractions). Starting materials and reagents were generally available from Sigma−Aldrich, Merck, TCI, Strem, or Lancaster Chemical Companies and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX, BDH, or Unilab Chemical Companies. Tetrahydrofuran (THF), MeOH, and CH_2Cl_2 were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.[15] Where necessary, reactions were performed under a nitrogen atmosphere.

Synthesis of 4,5-Dibromo-1*H*-pyrrole-2-carbaldehyde (6). In a modification of a published procedure,[4a] a magnetically stirred solution of commercially available 1*H*-pyrrole-2-carbaldehyde (**5**) (5.00 g, 52.6 mmol) in anhydrous THF (200 mL) and protected from light using aluminum foil was cooled to −78 °C, then treated with NBS (20.60 g, 115.7 mmol). The cooling bath was then removed, and the reaction mixture allowed to warm to 22 °C, stirred at this temperature for 20 h, then recooled to 0 °C and treated with Na_2SO_3 (14.00 g, 111.08 mmol). The resulting mixture was stirred at 0 °C for 0.5 h, then filtered through a pad of diatomaceous earth. The filtrate was concentrated under reduced pressure to give a brown oil, and subjecting this material to flash chromatography (silica, 1:19 → 1:9 v/v EtOAc/40−60 petroleum ether gradient elution) afforded, after concentration of the appropriate fractions (R_f = 0.4 in 1:4 v/v EtOAc/40−60 petroleum ether elution), 4,5-dibromo-1*H*-pyrrole-2-carbaldehyde (**6**)[4a] (11.0 g, 83%): pink, crystalline solid; the ^{1}H and ^{13}C NMR spectroscopic data acquired on this material matched those reported[4a] previously.

Synthesis of 4,5-Bis(4-methoxyphenyl)-1*H*-pyrrole-2-carbaldehyde (8). In a modification of a published procedure,[4a] a magnetically stirred mixture of 4,5-dibromo-1*H*-pyrrole-2-carbaldehyde (**6**) (4.90 g, 19.38 mmol), (4-methoxyphenyl)boronic acid (**7**) (8.83 g, 58.13 mmol), $Pd(PPh_3)_4$ (820 mg, 0.71 mmol), and Na_2CO_3 (12.32 g, 116.24 mmol) in deoxygenated 1,2-dimethoxyethane/H_2O (198 mL of a 6:1 v/v mixture) was heated at 85 °C under a nitrogen atmosphere for 20 h, then cooled to 22 °C before being poured into H_2O (200 mL) and extracted with EtOAc (3 × 150 mL). The combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 3:17 v/v EtOAc/40−60 petroleum ether elution). Concentration of the appropriate fractions (R_f = 0.6 3:7 v/v EtOAc/40−60 petroleum ether elution) gave 4,5-bis(4-methoxyphenyl)-1*H*-pyrrole-2-carbaldehyde (**8**) (5.00 g, 85%): yellow, crystalline solid; the ^{1}H and ^{13}C NMR spectroscopic data acquired on this material matched those reported[4a] previously.

Synthesis of 1-(4,5-Bis(4-methoxyphenyl)-1*H*-pyrrol-2-yl)-2-methylpropan-1-ol (9). In a modification of a published procedure,[4a] a magnetically stirred solution of 4,5-bis(4-methoxyphenyl)-1*H*-pyrrole-2-carbaldehyde (**8**) (922 mg, 3.00 mmol) in anhydrous THF (60 mL) maintained at 0 °C under an atmosphere of nitrogen was treated, dropwise over 0.08 h, with isopropylmagnesium bromide solution (3.75 mL of a 2.4 M solution in 2-methyltetrahydrofuran, 9.00 mmol). The ensuing mixture was stirred at 0 °C for 1 h,

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then quenched by the slow addition of ice (***CAUTION!*** *EXOTHERMIC REACTION*). The ensuing mixture was poured into H_2O (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:9 v/v EtOAc/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.7, 2-fold elution in 3:7 v/v EtOAc/40−60 petroleum ether), alcohol **9** (999 mg, 95%): clear, colorless oil; ^{1}H NMR (400 MHz, CD_3OD) δ 7.23 (m, 2H), 7.17 (m, 2H), 6.83−6.74 (complex m, 4H), 6.10 (s, 1H), 4.31 (d, J = 7.5 Hz, 1H), 3.76−3.74 (complex m, 6H), 2.05 (m, 1H), 1.06 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H) (signals due to OH and NH groups protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 159.6, 158.9, 135.1, 131.6, 130.3, 129.9, 128.1, 128.0, 121.6, 114.8, 114.6, 108.3, 75.0, 55.6, 35.5, 19.6, 19.3 (one signal obscured or overlapping); IR ν_{max} 3404, 2958, 2835, 1519, 1245, 1178, 1033, 833 cm^{-1}; MS (EI, 70 eV) m/z 351 ($M^{+\bullet}$, 100), 349 (90); HRMS m/z 351.1836 $M^{+\bullet}$ (calcd for $C_{22}H_{25}NO_3$, 351.1834).

Synthesis of 5-Isobutyl-2,3-bis(4-methoxyphenyl)-1*H*-pyrrole (10). $LiAlH_4$ (650 mg, 17.13 mmol) was added to a magnetically stirred solution of alcohol **9** (2.15 g, 6.12 mmol) in THF (108 mL) maintained at 22 °C under an atmosphere of nitrogen. The resulting mixture was stirred magnetically while being heated under reflux for 16 h. After this time the reaction mixture was cooled to 0 °C, then quenched by the slow addition of ice (***CAUTION!*** *EXOTHERMIC REACTION AND POSSIBILITY OF HYDROGEN EVOLUTION*). The ensuing mixture was poured into H_2O (200 mL) and extracted with EtOAc (3 × 150 mL), and the combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:9 v/v EtOAc/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.5 in 3:7 v/v EtOAc/40−60 petroleum ether elution), 5-isobutyl-2,3-bis(4-methoxyphenyl)-1*H*-pyrrole (**10**)[4a] (1.95 g, 95%): pink, crystalline solid; the ^{1}H and ^{13}C NMR spectroscopic data acquired on this material matched those reported[4a] previously.

Synthesis of 2,2′-Diisobutyl-4,4′,5,5′-tetrakis(4-methoxyphenyl)-1*H*,1′*H*-3,3′-bipyrrole (11). A magnetically stirred solution of 5-isobutyl-2,3-bis(4-methoxyphenyl)-1*H*-pyrrole (**10**) (120 mg, 0.36 mmol) in CH_2Cl_2 (40 mL) was treated with 4-methylmorpholine *N*-oxide (46 mg, 0.39 mmol) and molecular sieves (80 mg of powdered and activated 4 Å material), then tetra-*n*-propylammonium perruthenate (TPAP) (25 mg, 0.07 mmol). The resulting mixture was stirred at 22 °C for 96 h and then filtered through a pad of diatomaceous earth. The filtrate was concentrated under reduced pressure to give a black oil. Subjection of this material to flash chromatography (silica, 1:19 → 1:9 v/v EtOAc/30−40 petroleum ether gradient elution) afforded two fractions, A and B.

Concentration of fraction A (R_f = 0.5 in 3:7 v/v EtOAc/40−60 petroleum ether) gave compound **10** (80 mg, 67% recovery): pink solid; identical, in all respects, with an authentic sample.

Concentration of fraction B (R_f = 0.4 in 3:7 v/v EtOAc/40−60 petroleum ether) gave compound **11** (38 mg, 32% or 98% brsm): white, crystalline solid, mp 160−162 °C; ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 9.55 (s, 2H), 7.20 (d, J = 9.0 Hz, 4H), 6.98 (d, J = 9.0 Hz, 4H), 6.76 (d, J = 9.0 Hz, 4H), 6.66 (d, J = 9.0 Hz, 4H), 3.75 (s, 6H), 3.71 (s, 6H), 2.23−2.08 (complex m, 4H), 1.85 (m, 2H), 0.78 (d, J = 6.6 Hz, 6H), 0.73 (d, J = 6.5 Hz, 6H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 158.5, 158.3, 132.0, 131.3, 130.9, 128.8, 128.0, 126.5, 122.5, 116.4, 114.3, 113.8, 55.4, 55.3, 36.7, 28.6, 23.1, 23.0; IR ν_{max} 3383, 2954, 2834, 1514, 1286, 1242, 1176, 1033, 832 cm^{-1}; MS (EI, 70 eV) m/z 669 (50%), 668 ($M^{+\bullet}$, 100), 625 (20), 624 (45); HRMS m/z 668.3626 $M^{+\bullet}$ (calcd for $C_{44}H_{48}N_2O_4$, 668.3614).

Synthesis of 2-Isobutyl-2-methoxy-4,5-bis(4-methoxyphenyl)-1,2-dihydro-3*H*-pyrrol-3-one (12), (*Z*)-*N*-(1,2-Bis(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)-3-methylbutanamide (13), (*E*)-*N*-(1,2-Bis(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)-3-methylbutanamide (14), and 1,2-Bis(4-methoxyphenyl)ethane-1,2-dione (15). A magnetically stirred solution of compound **10** (1.00 g, 2.98 mmol) in CH_2Cl_2/MeOH (80 mL of a 1:1 v/v mixture) maintained at 22 °C and protected from light using aluminum foil was treated with MoOPH[6] (5.18 g, 11.9 mmol). The reaction mixture was stirred at 22 °C for 16 h, then quenched with H_2O (30 mL) before being diluted with EtOAc (50 mL). The ensuing mixture was filtered through a pad of diatomaceous earth, and the separated aqueous phase associated with the filtrate was extracted with EtOAc (3 × 100 mL). The combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:9 → 3:7 v/v EtOAc/40−60 petroleum ether gradient elution) to give three fractions, A−C.

Concentration of fraction A (R_f = 0.1 in 3:7 v/v EtOAc/40−60 petroleum ether) gave compound **12** (268 mg, 24%): yellow, crystalline solid, mp 125−127 °C; ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 7.54 (d, J = 9.0 Hz, 2H), 7.12 (d, J = 9.0 Hz, 2H), 6.98 (d, J = 9.0 Hz, 2H), 6.92 (s, 1H), 6.81 (d, J = 9.0 Hz, 2H), 3.85 (s, 3H), 3.77 (s, 3H), 3.16 (s, 3H), 1.89−1.76 (complex m, 3H), 0.92 (d, J = 6.5 Hz, 6H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 199.0, 171.7, 163.0, 158.9, 131.1, 131.0, 125.7, 124.6, 114.8, 114.2, 111.3, 92.3, 55.8, 55.4, 50.7, 46.2, 24.8, 24.6, 24.3; IR ν_{max} 3257, 2957, 1605, 1498, 1463, 1251, 1175, 1029, 836 cm^{-1}; MS (ESI, + ve) m/z 404 [$(M + Na)^+$, 100%], 382 [$(M + H)^+$, 15]; HRMS m/z 382.2016 $[M + H]^+$ (calcd for $C_{23}H_{28}NO_4$, 382.2013).

Concentration of fraction B (R_f = 0.2 in 3:7 v/v EtOAc/40−60 petroleum ether) gave a ca. 1:1 mixture of compounds **13** and **14** (160 mg, 15%): yellow, crystalline solid, mp 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.81 (s, 1H), 9.62 (s, 1H), 9.47 (s, 1H), 7.39 (d, J = 9.0 Hz, 2H), 7.18 (d, J = 9.0 Hz, 2H), 7.11 (s, 1H), 7.03−6.95 (complex m, 6H), 6.89 (d, J = 9.0 Hz, 2H), 6.74−6.68 (complex m, 4H), 3.86 (s, 3H), 3.85 (s, 3H), 3.75(0) (s, 3H), 3.74(7) (s, 3H), 2.30 (d, J = 7.1 Hz, 2H), 2.18 (m, 1H), 1.98 (m, 3H), 1.00 (d, J = 6.6 Hz, 6H), 0.88 (d, J = 6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 192.3, 171.8, 170.9, 161.5, 160.1, 159.7, 158.5, 153.8, 151.7, 131.9, 131.8(0), 131.7(7), 130.7, 128.3, 127.3, 126.6, 125.3, 125.2, 120.1, 114.7, 113.9(9), 113.9(8), 113.4, 55.5(1), 55.4(8), 55.3, 55.2, 47.6, 46.7, 26.0, 25.9, 22.6, 22.5; IR ν_{max} 3273, 2959, 1665, 1604, 1510, 1464, 1248, 1176, 1030, 833 cm^{-1}; MS (ESI, + ve) m/z 757 [$(2M + Na)^+$, 25%], 390 [$(M + Na)^+$, 50], 368 [$(M + H)^+$, 25], 284 (100); HRMS m/z 368.1860 $[M + H]^+$ (calcd for $C_{22}H_{26}NO_4$, 368.1856).

Concentration of fraction C (R_f = 0.3 in 3:7 v/v EtOAc/40−60 petroleum ether) gave benzil **15**[12] (410 mg, 51%): yellow solid, mp = 130−132 °C (lit.[12] mp 132−133 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 9.0 Hz, 4H), 6.97 (d, J = 9.0 Hz, 4H), 3.88 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 165.0, 132.5, 126.5, 114.4, 55.8; IR ν_{max} 1657, 1598, 1573, 1510, 1263, 1162, 1018, 880, 832 cm^{-1}; MS (EI, 70 eV) m/z 270 ($M^{+\bullet}$, 15%), 136 (85), 135 (100), 107 (35), 92 (70), 77 (75), 64 (30); HRMS m/z 270.0894 $M^{+\bullet}$ (calcd for $C_{16}H_{14}O_4$, 270.0892).

Synthesis of 2-Hydroxy-2-isobutyl-4,5-bis(4-methoxyphenyl)-1,2-dihydro-3*H*-pyrrol-3-one (16). A magnetically stirred solution of 2-isobutyl-2-methoxy-4,5-bis(4-methoxyphenyl)-1,2-dihydro-3*H*-pyrrol-3-one (**12**) (20 mg, 0.05 mmol) in CH_2Cl_2/H_2O (480 μL of a 4:1 v/v mixture) maintained at 0 °C under a nitrogen atmosphere was treated, dropwise over 0.08 h, with trifluoroacetic acid (200 uL, 2.61 mmol). The ensuing mixture was stirred at 0 °C for 25 min, and then H_2O (10 mL) followed by EtOAc (10 mL) were added at the same temperature. The separated organic phase was washed, at 0 °C, with H_2O (1 × 10 mL) and then $NaHCO_3$ (2 × 10 mL of a saturated aqueous solution) until the pH of the aqueous washings was between 5 and 7. The organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:1 v/v EtOAc/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.2 in 1:1 v/v EtOAc/40−60 petroleum ether), compound **16** (18 mg, 93%): light yellow oil; ^{1}H NMR (400 MHz, CD_3OD) δ 7.46 (d, J = 9.0 Hz, 2H), 7.06 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 6.83 (d, J = 9.0 Hz, 2H), 3.83 (s, 3H), 3.77 (s, 3H), 1.88 (d, J = 6.1 Hz, 2H), 1.71 (m, 1H), 0.97 (d, J = 6.5 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H) (signals due to OH and NH groups

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protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 202.3, 174.1, 163.9, 159.6, 131.8, 131.6, 126.0, 124.4, 115.0, 114.7, 108.8, 88.9, 56.0, 55.6, 46.7, 25.1, 24.7, 24.6; IR ν_{max} 3286, 2956, 1651, 1606, 1524, 1497, 1251, 1176, 1030, 837 cm^{-1}; MS (ESI, + ve) m/z 757 [(2M + Na)$^+$, 100%], 390 [(M + Na)$^+$, 45], 368 [(M + H)$^+$, 15]; HRMS m/z 368.1861 [M + H]$^+$ (calcd for $C_{22}H_{26}NO_4$, 368.1856).

Synthesis of (*Z*)-4,5-Bis(4-methoxyphenyl)-2-(2-methylpropylidene)-1,2-dihydro-3*H*-pyrrol-3-one (17). A magnetically stirred solution of 2-isobutyl-2-methoxy-4,5-bis(4-methoxyphenyl)-1,2-dihydro-3*H*-pyrrol-3-one (**12**) (30 mg, 0.08 mmol) in CH_2Cl_2/H_2O (710 μL of a 4:1 v/v mixture) maintained at 0 °C under a nitrogen atmosphere was treated, dropwise over 5 min, with trifluoroacetic acid (300 μL, 3.91 mmol). The ensuing mixture was stirred at 0 °C for 1 h, then warmed to 22 °C, and stirred at this temperature for a further 2.5 h. The mixture thus obtained was then quenched with H_2O (1 × 10 mL), before being extracted with EtOAc (2 × 15 mL). The combined organic phases were washed with H_2O (1 × 20 mL) and $NaHCO_3$ (2 × 10 mL of a saturated aqueous solution) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:9 → 3:17 v/v EtOAc/40−60 petroleum ether gradient elution) to give, after concentration of the appropriate fractions (R_f = 0.5 in 1:1 v/v EtOAc/40−60 petroleum ether), compound **17** (24 mg, 87%): light orange oil; ^{1}H NMR (600 MHz, CD_3OD) δ 7.47 (d, J = 9.0 Hz, 2H), 7.09 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 6.84 (d, J = 9.0 Hz, 2H), 6.08 (d, J = 10.5 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 2.98 (m, 1H), 1.18 (d, J = 6.5 Hz, 6H) (signal due to NH group proton not observed); ^{13}C NMR (150 MHz, CD_3OD) δ 186.5, 165.8, 163.6, 159.8, 137.6, 132.0, 131.6, 129.3, 125.9, 124.1, 115.0, 114.8, 113.6, 55.9, 55.7, 28.1, 22.8; IR ν_{max} 2961, 1602, 1578, 1496, 1433, 1252, 1175, 1032, 832 cm^{-1}; MS (ESI, + ve) m/z 721 [(2M + Na)$^+$, 100%], 350 [(M + H)$^+$, 65]; HRMS m/z 350.1751 [M + H]$^+$ (calcd for $C_{22}H_{24}NO_3$, 350.1751).

Synthesis of 4,4′-(5-Isobutyl-1*H*-pyrrole-2,3-diyl)diphenol (18). A magnetically stirred solution of compound **10** (1.00 g, 2.98 mmol) in anhydrous CH_2Cl_2 (200 mL) maintained at −78 °C under an atmosphere of nitrogen was treated, dropwise over 0.17 h, with boron tribromide (2.2 mL, 23.62 mmol). The ensuing mixture was left to warm to 22 °C over 20 h and then quenched by the slow addition of ice (***CAUTION!*** *EXOTHERMIC REACTION*). The ensuing mixture was poured into H_2O (200 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:4 v/v EtOAc/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.5 in 1:1 v/v EtOAc/40−60 petroleum ether), compound **18** (800 mg, 87%): light yellow oil; ^{1}H NMR (400 MHz, CD_3OD) δ 7.14 (d, J = 9.0 Hz, 2H), 7.09 (d, J = 9.0 Hz, 2H), 6.67 (m, 4H), 5.86 (s, 1H), 2.45 (d, J = 7.1 Hz, 2H), 1.91 (m, 1H), 0.97 (d, J = 6.5 Hz, 6H), (signals due to OH and NH groups protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 156.6, 155.9, 132.5, 130.9, 130.3, 129.8, 127.4, 127.3, 121.5, 116.0, 115.9, 108.6, 38.1, 30.4, 22.9; IR ν_{max} 3363, 2955, 2868, 1699, 1519, 1433, 1365, 1227, 1171, 834 cm^{-1}; MS (EI, 70 eV) m/z 307 (M$^{+\bullet}$, 20%), 264 (100); HRMS m/z 307.1573 M$^{+\bullet}$ (calcd for $C_{20}H_{21}NO_2$, 307.1572).

Synthesis of (5-Isobutyl-1*H*-pyrrole-2,3-diyl)bis(4,1-phenylene) Diacetate (19). A magnetically stirred solution of compound **18** (690 g, 2.24 mmol) in dry CH_2Cl_2 (42 mL) maintained at 0 °C under an atmosphere of nitrogen was treated with triethylamine (940 μL, 6.74 mmol) and acetyl chloride (800 μL, 11.25 mmol). After being maintained at 0 °C for a further 0.5 h the reaction mixture was quenched with H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 3:17 v/v EtOAc/40−60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.3 in 3:7 v/v EtOAc/40−60 petroleum ether), compound **19** (843 mg, 96%): clear, colorless oil; ^{1}H NMR [400 MHz, $(CD_3)CO$] δ 10.01 (s, 1H), 7.34 (m, 4H), 7.02 (m, 4H), 6.05 (d, J = 2.7 Hz, 1H), 2.52 (d, J = 7.1 Hz, 2H), 2.24(3) (s, 3H), 2.24(2) (s, 3H), 1.97 (m, 1H), 0.97 (d, J = 6.5 Hz, 6H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 169.6(9), 169.6(7), 150.2, 149.8, 136.0, 133.6, 132.4, 129.7, 129.0, 126.6, 122.6, 122.4, 121.8, 109.4, 37.6, 22.8, 21.0(0), 20.9(8) (one signal obscured or overlapping); IR ν_{max} 3377, 2956, 1747, 1514, 1369, 1217, 1196, 1015, 912, 848 cm^{-1}; MS (EI, 70 eV) m/z 391 (M$^{+\bullet}$, 50%), 348 (35), 306 (100), 264 (70), 234 (30); HRMS m/z 391.1791 M$^{+\bullet}$ (calcd for $C_{24}H_{25}NO_4$, 391.1784).

Synthesis of (5-Isobutyl-5-methoxy-4-oxo-4,5-dihydro-1*H*-pyrrole-2,3-diyl)bis(4,1-phenylene) Diacetate (20) and Oxalylbis(4,1-phenylene) Diacetate (21). A magnetically stirred solution of compound **19** (1.00 g, 2.98 mmol) in CH_2Cl_2/MeOH (80 mL of a 1:1 v/v mixture) maintained at 22 °C and protected from light with aluminum foil was treated with MoOPH[6] (5.18 g, 11.9 mmol). The ensuing mixture was stirred at 22 °C for 16 h, then quenched with H_2O (30 mL) before being diluted with EtOAc (1 × 50 mL), then filtered through a pad of diatomaceous earth. The separated aqueous phase associated with the filtrate was extracted with EtOAc (3 × 100 mL), and the combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:9 → 3:7 v/v EtOAc/40−60 petroleum ether gradient elution) to give two fractions, A and B.

Concentration of fraction A (R_f = 0.2, eluted twice with 3:7 v/v EtOAc/40−60 petroleum ether) gave compound **20** (324 mg, 29%): yellow, crystalline solid, mp 79−81 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.59 (d, J = 8.7 Hz, 2H), 7.19 (m, 4H), 7.00 (d, J = 8.7 Hz, 2H), 3.23 (s, 3H), 2.29 (s, 3H), 2.25 (s, 3H), 1.87 (m, 2H), 1.77 (m, 1H), 0.96 (m, 6H) (signal due to NH group proton not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 201.0, 175.2, 171.2, 170.6, 154.9, 150.6, 131.2, 131.1, 130.5, 129.5, 123.5, 122.6, 111.3, 93.8, 51.3, 46.4, 24.8(4), 24.7(5), 24.7, 20.9(1), 20.8(8); IR ν_{max} 3270, 2958, 1754, 1663, 1518, 1370, 1198, 1167, 1016, 912 cm^{-1}; MS (EI, 70 eV) m/z 437 (M$^{+\bullet}$, 55%), 407 (50), 364 (45), 322 (45), 252 (65), 210 (100); HRMS m/z 437.1837 M$^{+\bullet}$ (calcd for $C_{25}H_{27}NO_6$, 437.1838).

Concentration of fraction B (R_f = 0.5, eluted twice with 3:7 v/v EtOAc/40−60 petroleum ether) gave compound **21**[13] (391 mg, 47%): pale yellow, crystalline solid, mp 88−90 °C; ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 8.06 (d, J = 8.7 Hz, 4H), 7.39 (d, J = 8.7 Hz, 4H), 2.31 (s, 6H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 194.1, 169.2, 157.1, 132.3, 131.2, 123.7, 21.0; IR ν_{max} 1760, 1671, 1596, 1369, 1187, 1155, 1013, 911, 665 cm^{-1}; MS (ESI, + ve) m/z 349 [(M + Na)$^+$, 100%]; HRMS m/z 349.0686 (M + Na)$^+$ (calcd for $C_{18}H_{14}O_6Na$, 349.0683).

Synthesis of 4,5-Bis(4-hydroxyphenyl)-2-isobutyl-2-methoxy-1,2-dihydro-3*H*-pyrrol-3-one (24). A magnetically stirred solution of compound **20** (98 mg, 0.22 mmol) in MeOH (10 mL) maintained at 0 °C was treated, in one portion, with potassium carbonate (34 mg, 0.25 mmol). The ensuing mixture was maintained at 0 °C for 1 h, then treated with H_2O (20 mL) before being concentrated under reduced pressure. The residue thus obtained was extracted with EtOAc (3 × 50 mL), and the combined organic phases were then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a yellow solid. This material was subjected to flash column chromatography (silica, 1:1 v/v EtOAc/40−60 petroleum ether elution) and gave, after concentration of the appropriate fractions (R_f = 0.1 in 1:1 v/v EtOAc/40−60 petroleum ether), compound **24** (77 mg, 97%): yellow, crystalline solid, mp 124−126 °C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.42 (d, J = 9.0 Hz, 2H), 6.96 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 9.0 Hz, 2H), 6.71 (d, J = 9.0 Hz, 2H), 3.20 (s, 3H), 1.84 (m, 2H), 1.73 (m, 1H), 0.95 (d, J = 6.5 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H) (signals due to OH and NH groups protons not observed); ^{13}C NMR (150 MHz, CD_3OD) δ 200.7, 175.6, 162.5, 157.1, 131.9, 131.8, 124.5, 122.7, 116.4, 116.2, 111.7, 93.5, 51.1, 46.4, 24.8, 24.7(2), 24.7(0); IR ν_{max} 3250, 2957, 2930, 1647, 1605, 1587, 1526, 1492, 1428, 1236, 1172, 834 cm^{-1}; MS (ESI, + ve) m/z 376 [(M + Na)$^+$, 100%], 354 [(M + H)$^+$, 10]; HRMS m/z 354.1705 (M + H)$^+$ (calcd for $C_{21}H_{24}NO_4$, 354.1700).

Synthesis of Discoipyrrole C (3). A magnetically stirred solution of 4,5-bis(4-hydroxyphenyl)-2-isobutyl-2-methoxy-1,2-dihydro-3*H*-pyrrol-3-one (**24**) (61 mg, 0.17 mmol) in CH_2Cl_2/H_2O (6.65 mL of a 4:1 v/v mixture) maintained at 0 °C under a nitrogen atmosphere

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was treated, dropwise over 5 min, with trifluoroacetic acid (670 μL, 8.75 mmol). The ensuing mixture was stirred at 0 °C for 25 min, and then H_2O (10 mL) followed by EtOAc (10 mL) were added at the same temperature. The separated organic phase was washed, at 0 °C, with H_2O (1 × 10 mL), then $NaHCO_3$ (2 × 10 mL of a saturated aqueous solution), until the pH of the aqueous washings was between 5 and 7. The separated organic layer was dried (Na_2SO_4), filtrated, and concentrated under reduced pressure, and the residue thus obtained was subjected to flash column chromatography (silica, 1:1 v/v EtOAc/40−60 petroleum ether elution). Concentration of the appropriate fractions (R_f = 0.1, eluted twice in 1:1 v/v EtOAc/40−60 petroleum ether) then gave discoipyrrole C (**3**) (52 mg, 89%): light yellow solid, no melting point (decomposition above 141 °C); ^{1}H NMR (400 MHz, CD_3OD) δ 7.38 (d, *J* = 9.0 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 6.76 (d, *J* = 9.0 Hz, 2H), 6.70 (d, *J* = 9.0 Hz, 2H), 1.87 (d, *J* = 6.1 Hz, 2H), 1.69 (m, 1H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.94 (d, *J* = 6.5 Hz, 3H) (signals due to OH and NH groups protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 202.2, 174.4, 162.2, 156.9, 131.9, 131.8, 125.0, 123.1, 116.3, 116.1, 108.9, 88.8, 46.7, 25.1, 24.7, 24.6; IR ν_{max} 3278, 2958, 1606, 1527, 1492, 1429, 1234, 837 cm^{-1}; MS (ESI, + ve) *m*/*z* 701 [(2M + Na)$^+$, 65%], 362 [(M + Na)$^+$, 100], 340 [(M + H)$^+$, 15]; HRMS *m*/*z* 340.1548 (M + H)$^+$ (calcd for $C_{20}H_{22}NO_4$, 340.1543).

Synthesis of (*Z*)-4,5-Bis(4-methoxyphenyl)-2-(2-methylpropylidene)-1,2-dihydro-3*H*-pyrrol-3-one (25). A magnetically stirred solution of compound **24** (27 mg, 0.08 mmol) in CH_2Cl_2/H_2O (710 μL of a 4:1 v/v mixture) maintained at 0 °C under a nitrogen atmosphere was treated, dropwise over 5 min, with trifluoroacetic acid (280 uL, 3.66 mmol). The ensuing mixture was stirred at 0 °C for 1 h, then warmed to 22 °C and stirred at this temperature for another 2.5 h before being quenched with H_2O (1 × 10 mL), then extracted with EtOAc (2 × 15 mL). The combined organic phases were washed with H_2O (1 × 20 mL) and then $NaHCO_3$ (2 × 10 mL of a saturated aqueous solution) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:1 v/v EtOAc/40−60 petroleum ether elution) to give two fractions, A and B.

Concentration of fraction A (R_f = 0.1, eluted twice with 1:1 v/v EtOAc/40−60 petroleum ether) afforded discoipyrrole C (**3**) (9 mg, 35%): yellow solid that was identical, in all respects, with the material obtained earlier.

Concentration of fraction B (R_f = 0.1 in 1:1 v/v EtOAc/40−60 petroleum ether) afforded compound **25** (15 mg, 61%): light orange oil; ^{1}H NMR [600 MHz, $(CD_3)_2CO$] δ 8.23 (s, 1H), 7.43 (d, *J* = 9.0 Hz, 2H), 7.10 (d, *J* = 9.0 Hz, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 6.73 (d, *J* = 9.0 Hz, 2H), 5.81 (d, *J* = 10.3 Hz, 1H), 2.98 (m, 1H), 1.13 (d, *J* = 6.5 Hz, 6H) (signals due to OH groups protons not observed); ^{13}C NMR [150 MHz, $(CD_3)_2CO$] δ 185.6, 162.4, 160.6, 156.4, 136.8, 131.3, 131.1, 125.1, 123.7, 123.5, 116.2, 115.7, 113.1, 27.3, 22.8; IR ν_{max} 3200, 2962, 2869, 1691, 1526, 1491, 1456, 1348, 1236, 1172, 1067, 928, 835 cm^{-1}; MS (EI, 70 eV) *m*/*z* 321 (M$^{+\bullet}$, 100%), 319 (30), 280 (30), 210 (35); HRMS *m*/*z* 321.1365 M$^{+\bullet}$ (calcd for $C_{20}H_{19}NO_3$, 321.1365).

Crystallographic Data. *Compound 3:* crystals obtained as colorless masses from EtOAc/acetone/petroleum ether (40−60), $C_{20}H_{21}NO_4$, *M* = 339.38, *T* = 150 K, monoclinic, space group $P2_1/n$, *Z* = 4, *a* = 9.8726(1) Å, *b* = 12.6801(1) Å, *c* = 18.1414(2) Å; β = 92.315(1)°; *V* = 2269.19(4) Å^3, D_x = 0.993 g cm^{-3}, 4554 unique data ($2\theta_{max}$ = 147.6°), *R* = 0.034 [for 4193 reflections with $I > 2.0\sigma(I)$]; *Rw* = 0.092 (all data), *S* = 1.05.

Compound 11: crystals obtained as colorless masses from acetone/hexane, $C_{44}H_{48}N_2O_4{\cdot}2(C_3H_6O)$, *M* = 785.00, *T* = 150 K, monoclinic, space group $P2_1/n$, *Z* = 4, *a* = 19.2834(19) Å, *b* = 10.8405(9) Å, *c* = 24.0533(13) Å; β = 90.220(7)°; *V* = 5028.1(7) Å^3, D_x = 1.037 g cm^{-3}, 9690 unique data ($2\theta_{max}$ = 144.4°), *R* = 0.114 [for 4982 reflections with $I > 2.0\sigma(I)$]; *Rw* = 0.380 (all data), *S* = 1.13.

Compound 12: crystals obtained as colorless masses from EtOAc, $C_{23}H_{27}NO_4$, *M* = 381.45, *T* = 150 K, monoclinic, space group *C*2/*c*, *Z* = 8, *a* = 21.8292(3) Å, *b* = 15.8674(2) Å, *c* = 12.3179(2) Å; β = 91.099(1)°; *V* = 4265.80(11) Å^3, D_x = 1.188 g cm^{-3}, 4309 unique data ($2\theta_{max}$ = 147.6°), *R* = 0.036 [for 3920 reflections with $I > 2.0\sigma(I)$]; *Rw* = 0.099 (all data), *S* = 1.03.

Compound 13: crystals obtained as colorless masses from acetone $C_{22}H_{25}NO_4$, *M* = 367.43, *T* = 150 K, monoclinic, space group $P2_1/c$, *Z* = 8, *a* = 12.4371(1) Å, *b* = 14.4844(1) Å, *c* = 22.3921(2) Å; β = 98.146(1)°; *V* = 3993.10(6) Å^3, D_x = 1.222 g cm^{-3}, 8040 unique data ($2\theta_{max}$ = 147.6°), *R* = 0.039 [for 7086 reflections with $I > 2.0\sigma(I)$]; *Rw* = 0.105 (all data), *S* = 1.03.

Compound 14: crystals obtained as colorless masses from acetone $C_{22}H_{25}NO_4$, *M* = 367.43, *T* = 150 K, monoclinic, space group $P2_1/c$, *Z* = 8, *a* = 9.2101(3) Å, *b* = 20.2873(7) Å, *c* = 21.2870(11) Å; β = 96.731(4)°; *V* = 3950.0(3) Å^3, D_x = 1.236 g cm^{-3}, 8073 unique data ($2\theta_{max}$ = 52.8°), *R* = 0.048 [for 5212 reflections with $I > 2.0\sigma(I)$]; *Rw* = 0.119 (all data), *S* = 1.02.

Structure Determination. The image for compound **14** was measured on a diffractometer (Mo Kα, graphite monochromator, λ = 0.710 73 Å) fitted with an area detector, and the data were extracted using the DENZO/Scalepack package.[16] Images for compounds **3**, **11**, **12**, and **13** were measured on a diffractometer (Cu Kα, mirror monochromator, λ = 1.541 84 Å) fitted with an area detector, and the data were extracted using the CrysAlis package.[17] The structure solutions for all five compounds were solved with ShelXT[18] and refined using ShelXL[19] in the OLEX2 package.[20]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.7b00872.

Data derived from the single-crystal X-ray analyses of compounds **3**, **11**, **12**, **13**, and **14**; ^{1}H NMR spectra of compounds **6**, **8**, and **10**; ^{1}H and ^{13}C NMR spectra of compounds **3**, **9**, **11**−**21**, **24**, and **25** (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1573703, 1573704, 1573705, 1573706, and 1573707). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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