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# SYNTHESIS OF 4,5-DISUBSTITUTED PYRANO[3,4-*b*]PYRROL-7(1*H*)-ONES VIA SONOGASHIRA–HAGIHARA CROSS-COUPLING OF *N*-BENZENESULFONYL-3-BROMO-1*H*-PYRROLE-2-CARBOXYLATE AND SUBSEQUENT IODINE-MEDIATED CYCLIZATION

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**Abstract** – A method for the synthesis of 4,5-disubstituted pyrano[3,4-*b*]pyrrol-7-(1*H*)-ones has been developed in this study. The key reactions involved are the Sonogashira–Hagihara cross-coupling of methyl *N*-benzenesulfonyl-3-bromo-1*H*-pyrrole-2-carboxylate with terminal alkynes, followed by the iodine-mediated cyclization of 3-alkynylated *N*-benzenesulfonyl-1*H*-pyrrole-2-carboxylates. The thus-obtained 5-substituted 4-iodopyrano[3,4-*b*]pyrrol-7(1*H*)-ones could be converted to 4,5-disubstituted pyrano[3,4-*b*]pyrrol-7(1*H*)-ones via the Suzuki–Miyaura or Sonogashira–Hagihara cross-coupling reactions.

## INTRODUCTION

Heterocyclic compounds possessing a common pyrano[3,4-*b*]pyrrol-7(1*H*)-one ring system have been isolated from natural sources such as prosobranch mollusk, ascidians, and sponges.[1] These include lamellarins (A–Z, α–χ, and A1–A6, including their acetate and sulfate derivatives),[2] ningalins A, B, E, and F,[3] and bacliferin O[4] (Figure 1). Many of these natural products and their derivatives exhibit unique structures and significant biological activities. For instance, lamellarin D shows potent cytotoxicity against cancer cell lines, including multi-drug-resistant phenotypes.[5] The strong correlation observed between the cytotoxicity and topoisomerase I inhibition indicates that DNA topoisomerase I is a major molecular target of lamellarin D in cancer cells.[6] Lamellarin D also induces apoptosis of cancer cell lines by directly inhibiting the mitochondrial function.[7] In contrast, lamellarin N strongly inhibits

This paper is dedicated to Professor Dr. Kiyoshi Tomioka on the occasion of his 70th birthday.

several protein kinases, such as CDK1, CDK5, GSK-3, PIM1, and DYRK1A, relevant to cancer and neurodegenerative diseases,[8] whereas lamellarin α 20-sulfate and other related lamellarin sulfates exhibit anti-HIV-1 activities at noncytotoxic concentrations by inhibiting the virus entry[9] or integration steps.[2j,5c] In addition, ningalin B and its hexamethyl ether display multi-drug-resistance (MDR) reversal activity.[10] Due to their unique structures and significant biological activities, the synthesis of these compounds has attracted considerable amount of attention from organic and medicinal chemists in recent years. As a result, several synthetic methods have been developed hitherto.[11,12] Although these approaches are useful for the preparation of lamellarin and ningalin, most of them involve the construction of a 4,5-benzo-fused pyrano[3,4-*b*]pyrrol-7(1*H*)-one scaffold. In order to prepare various types of lamellarin and ningalin analogues for lead discovery and/or optimization in medicinal chemistry, it is necessary to develop methods via the construction of a non-benzo-fused pyrano[3,4-*b*]pyrrol-7(1*H*)-one scaffold. However, the construction of this scaffold has rarely been reported.[13] Herein, we describe the synthesis of 4,5-disubstituted pyrano[3,4-*b*]pyrrol-7(1*H*)-ones **1**, starting from the readily available methyl *N*-benzenesulfonyl-3-bromo-1*H*-pyrrole-2-carboxylate (**2**).[11o,14]

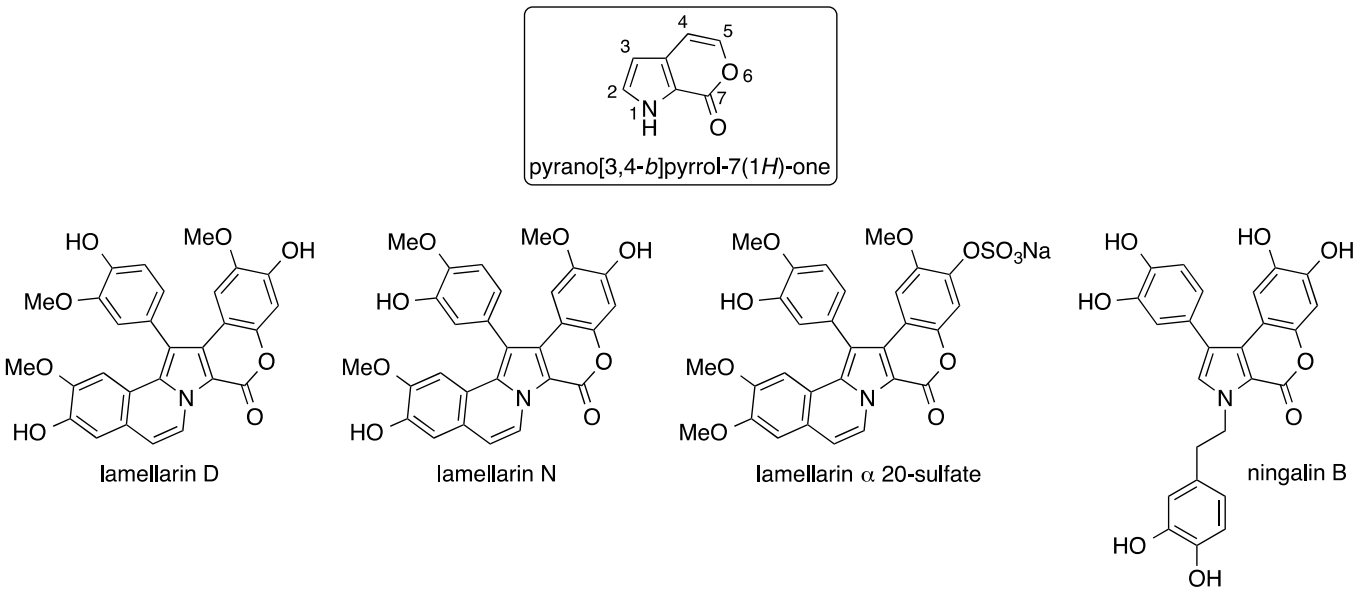
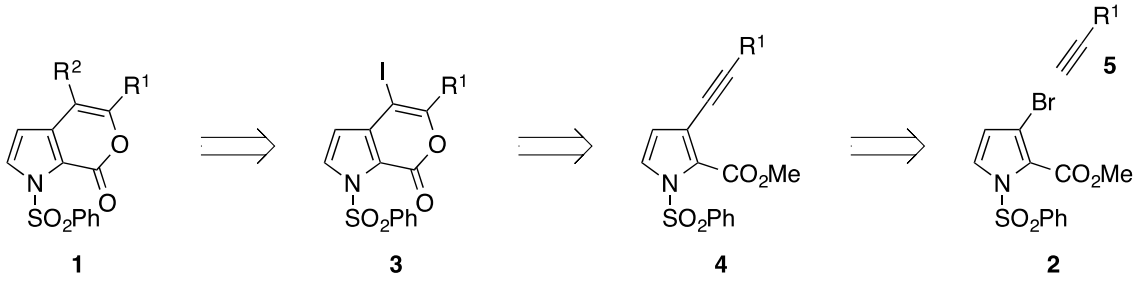



Figure 1. Examples of natural products possessing a common pyrano[3,4-*b*]pyrrol-7(1*H*)-one scaffold

## RESULTS AND DISCUSSION

The key step in the synthesis of 4,5-disubstituted pyrano[3,4-*b*]pyrrol-7(1*H*)-ones **1** from methyl *N*-benzenesulfonyl-3-bromo-1*H*-pyrrole-2-carboxylate (**2**) is the construction of a 2-pyrone ring at the 2- and 3-positions of the preexisting pyrrole ring. Yao and Larock reported the highly efficient synthesis of various substituted isocoumarins and 2-pyrones via the electrophilic cyclization of *o*-(1-alkynyl)benzoates and (*Z*)-2-alken-4-ynoates using iodine as an electrophilic source; we utilized this method in our synthesis.[15] The preparation of **1** from **2** is shown retrosynthetically in Scheme 1.

Compound **1** was obtained from 5-substituted 4-iodopyrano[3,4-*b*]pyrrol-7(1*H*)-one **3** by Pd-catalyzed reactions such as Suzuki–Miyaura and Sonogashira–Hagihara cross-couplings.[16,17] The 2-pyrone ring scaffold of **3** was constructed via the iodine-mediated 6-*endo-dig* electrophilic cyclization of 3-alkynylated pyrrole-2-carboxylate **4**.[18] Finally, 3-alkynylated pyrrole-2-carboxylate **4** was prepared from **2** via the Sonogashira–Hagihara cross-coupling with terminal alkynes **5**.

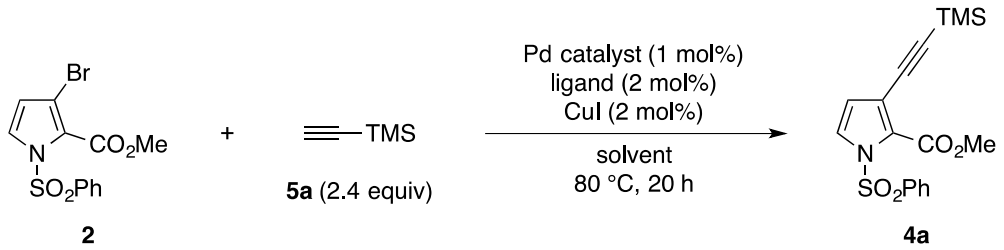



Scheme 1

Based on the retrosynthetic analysis, we first examined the Sonogashira–Hagihara cross-coupling of 3-bromopyrrole **2** with trimethylsilylacetylene (**5a**), the results of which are summarized in Table 1. Initially, various solvents were screened under the standard Sonogashira–Hagihara cross-coupling conditions [$Pd(PPh_3)_2Cl_2$ (1 mol%), CuI (2 mol%), 80 °C, 20 h] (entries 1–4).[19] The 3-(trimethylsilyl)ethynylated pyrrole **4a** was obtained in moderate yields (entries 1 and 2) using secondary diethylamine or bidentate *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) as a solvent. When the reaction was performed in tertiary diisopropylethylamine and triethylamine, the yield of **4a** was drastically improved to 90 and 92%, respectively (entries 3 and 4). Next, other Pd-based catalyst systems were screened using triethylamine as a solvent but the yield of product **4a** did not improve (entries 5–7).[20] Thus, the conditions shown in entry 4 were considered optimal.

Having established the optimal reaction conditions for the Sonogashira–Hagihara cross-coupling of 3-bromopyrrole **2**, we examined the Sonogashira–Hagihara cross-coupling of **2** with different terminal alkynes **5** (Table 2). Treatment of **2** with phenylacetylene (**5b**) (2.4 equiv) in the presence of $Pd(PPh_3)_2Cl_2$ (1 mol%) and CuI (2 mol%) in triethylamine at 80 °C for 20 h furnished **4b** in 95% yield (entry 1). However, the other terminal alkynes **5c–e** gave the 3-alkynylated products **4c–e** in modest yields, along with the unreacted **2** (entries 2–4). When propargyl alcohol (**5f**) was used, the desired product **4f** was not observed. Instead, starting material **2** was recovered in 24% yield, accompanied by the *N*-deprotected product **7** in 49% yield (entry 5). It is possible that compound **7** was produced by the nucleophilic attack of the alcohol on the sulfonyl group of **2**.

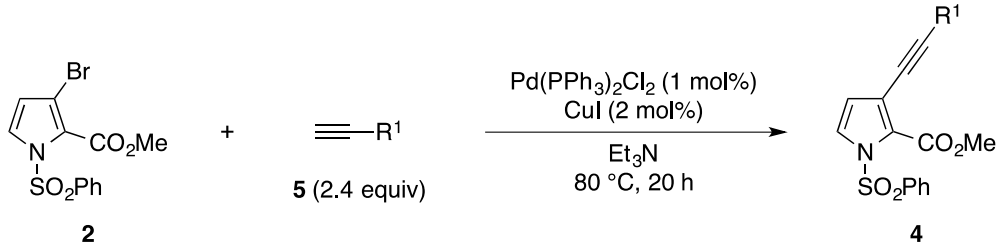
Table 1. Sonogashira–Hagihara cross-coupling of 3-bromopyrrole **2** with trimethylsilylacetylene (**5a**)




| entry | Pd catalyst | ligand | solvent | **4a** (%)[a] |
|---|---|---|---|---|
| 1 | $PdCl_2(PPh_3)_2$ | – | $Et_2NH$ | 63 |
| 2 | $PdCl_2(PPh_3)_2$ | – | TMEDA | 63 |
| 3 | $PdCl_2(PPh_3)_2$ | – | *i*-$Pr_2NEt$ | 90 |
| 4 | $PdCl_2(PPh_3)_2$ | – | $Et_3N$ | 92 |
| 5 | $Pd(PPh_3)_4$ | – | $Et_3N$ | 67 |
| 6 | $Na_2[PdCl_4]$ | $PPh_3$ | $Et_3N$ | 69 |
| 7 | $Na_2[PdCl_4]$ | **6**[b] | $Et_3N$ | 74 |

[a] Isolated yield. [b] 2-(Di-*t*-butylphosphino)-1-phenylindole (**6**).

Table 2. Sonogashira–Hagihara cross-coupling of 3-bromopyrrole **2** with terminal alkynes **5**



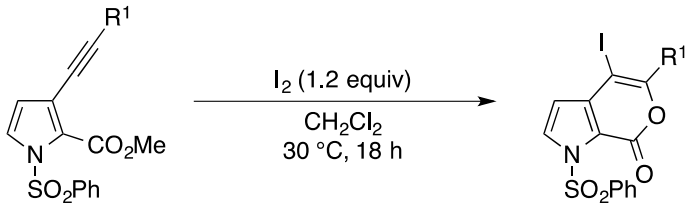

| entry | **5** | $R^1$ | **4** | **4** (%)[a] | **2** (%)[a] |
|---|---|---|---|---|---|
| 1 | **5b** | Ph | **4b** | 95 | 0 |
| 2 | **5c** | cyclohex-1-en-1-yl | **4c** | 33 | 56 |
| 3 | **5d** | *n*-Bu | **4d** | 47 | 51 |
| 4 | **5e** | $CH_2OTIPS$ | **4e** | 56 | 22 |
| 5 | **5f** | $CH_2OH$ | **4f** | 0 | 24[b] |

[a] Isolated yield. [b] Methyl 3-bromo-1*H*-pyrrole-2-carboxylate (**7**) was also obtained in 49% yield.

With several types of 3-alkynylated pyrrole-2-carboxylates **4** in hand, we attempted to convert them into 5-substituted 4-iodopyrano[3,4-*b*]pyrrol-7(1*H*)-ones **3**, the results of which are summarized in Table 3. When **4b** was treated with $I_2$ (1.2 equiv) in $CH_2Cl_2$ at 30 °C for 18 h, the cyclized

4-iodopyrano[3,4-*b*]pyrrol-7(1*H*)-one **3b** was obtained in 96% yield and no 5-*exo-dig* cyclization product was observed (entry 1). Under similar conditions, compounds **4c**–**e** gave the corresponding 4-iodopyrano[3,4-*b*]pyrrol-7(1*H*)-ones **3c**–**e** in good-to-excellent yields (entries 2–4). The cyclization of **4a** was slightly slower than the reaction of **4b**–**e** (entry 5). However, the yield of **3a** was improved to 79% on extending the reaction time to 120 h (entry 6). These results suggested that the ease of cyclization of 3-alkynylated pyrrole-2-carboxylate **4** depends on the steric hindrance around the alkynyl group.

Table 3. Iodine-mediated cyclization of 3-alkynylated pyrrole-2-carboxylate **4**



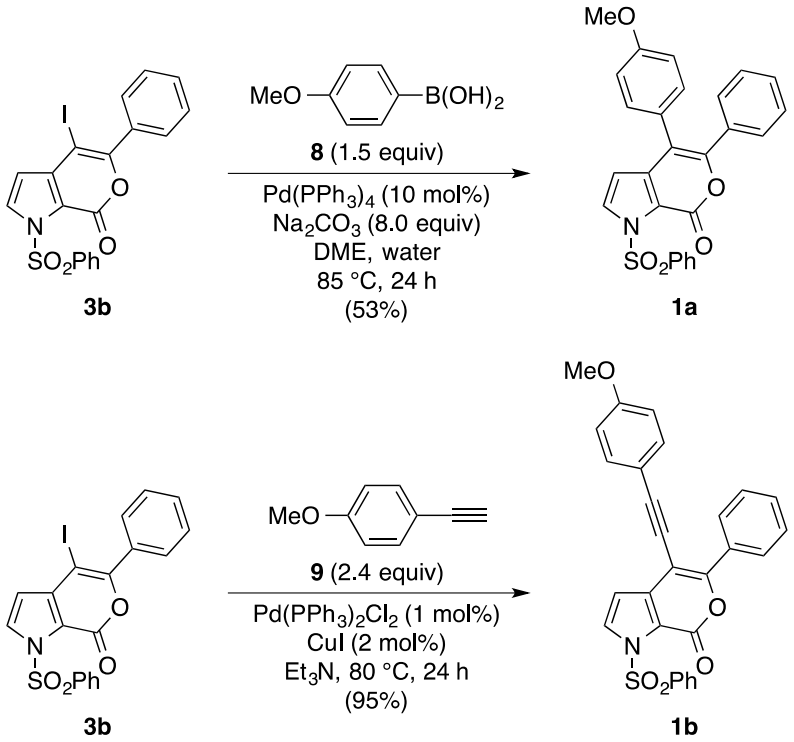

**4** **3**

| entry | **4** | $R^1$ | **3** | **3** (%)[a] | **4** (%)[a] |
|---|---|---|---|---|---|
| 1 | **4b** | Ph | **3b** | 96 | – |
| 2 | **4c** | cyclohex-1-en-1-yl | **3c** | 93 | – |
| 3 | **4d** | *n*-Bu | **3d** | 92 | – |
| 4 | **4e** | $CH_2OTIPS$ | **3e** | 74 | – |
| 5 | **4a** | TMS | **3a** | 62 | 27 |
| 6[b] | **4a** | TMS | **3a** | 79 | 12 |

[a] Isolated yield. [b] The reaction was carried out for 120 h.

After the 4-iodopyrano[3,4-*b*]pyrrol-7(1*H*)-ones **3** were obtained, further conversion to 4,5-disubstituted pyrano[3,4-*b*]pyrrol-7(1*H*)-ones **1** was attempted (Scheme 2). For example, 4-iodo-5-phenyl-pyrano[3,4-*b*]pyrrol-7(1*H*)-one (**3b**) gave the corresponding C-4 substituted products **1a** and **1b** in good-to-excellent yields via the Suzuki–Miyaura and Sonogashira–Hagihara cross-coupling reactions.

In conclusion, we have developed a method for the synthesis of 4,5-disubstituted pyrano[3,4-*b*]pyrrol-7(1*H*)-ones (**1**). Key steps to this approach are the Sonogashira–Hagihara cross-coupling of methyl *N*-benzenesulfonyl-3-bromo-1*H*-pyrrole-2-carboxylate (**2**), followed by the iodine-mediated 6-*endo-dig*




Scheme 2

electrophilic cyclization. This method may be utilized for the synthesis of various bioactive natural products and their analogues possessing the pyrano[3,4-*b*]pyrrol-7(1*H*)-one scaffold. Further studies to expand the scope of this method are in progress in our laboratory.

## EXPERIMENTAL

The melting points were determined with a Yanagimoto micro melting point apparatus and were reported as obtained. IR spectra were obtained with a Thermo Nicolet Nexus 670 NT FT-IR instrument and are reported in terms of the absorption frequency ($cm^{-1}$). NMR spectra were recorded on a JEOL JNM-AL400 instrument (400 MHz for $^1H$ and 100 MHz for $^{13}C$ NMR spectroscopies) or a Varian NMR System 500PS SN instrument (500 MHz for $^1H$ and 126 MHz for $^{13}C$ NMR spectroscopies). Chemical shifts for $^1H$ NMR were expressed in parts per million (ppm) relative to tetramethylsilane ($\delta$0.0 ppm). The data from the $^1H$ NMR spectra are reported as follows: chemical shift ($\delta$ ppm), multiplicity (s = singlet, d = doublet, dd = double doublet, t = triplet, sep = septet, m = multiplet, br s = broad singlet), coupling constant (Hz), and integration. Chemical shifts for $^{13}C$ NMR are expressed in ppm relative to tetramethylsilane ($\delta$0.0 ppm), $^{13}C$ NMR data are reported in terms of only chemical shift. HMQC and HMBC spectra were recorded on a Varian NMR System 500PS SN instrument. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-700N (fast atom bombardment mass spectrometry, FABMS) instrument. Column chromatography was conducted using silica gel 60N, 63–210 μm (Kanto Chemical Co., Inc.) or

Chromatorex NH-DM1020 (Fuji Silysia Chemical Ltd.). Flash chromatography was conducted using silica gel 60N, 40–50 μm (Kanto Chemical Co., Inc.).

**Typical procedure for Sonogashira–Hagihara cross-coupling of methyl *N*-benzenesulfonyl-3-bromo-1*H*-pyrrole-2-carboxylate (2) with trimethylsilylacetylene (5a) (Table 1).** Under an argon atmosphere, a mixture of methyl *N*-benzenesulfonyl-3-bromo-1*H*-pyrrole-2-carboxylate (**2**) (344 mg, 1.00 mmol), trimethylsilylacetylene (**5a**) (339 μL, 2.40 mmol), CuI (3.8 mg, 20 μmol), an appropriate Pd-based catalyst (10 μmol), and an appropriate solvent (1.0 mL) was heated in a sealed tube at 80 °C for 20 h. After cooling to rt, the mixture was diluted with $CH_2Cl_2$ and evaporated. The residue was diluted with $CH_2Cl_2$ and the mixture was washed with water and brine, dried over $Na_2SO_4$, and evaporated. The residue was purified by column chromatography over silica gel 60N (hexane–EtOAc = 5:1) to give **4a**. The results are summarized in Table 1.

**Methyl *N*-(benzenesulfonyl)-3-[2-(trimethylsilyl)ethynyl]-1*H*-pyrrole-2-carboxylate (4a).** Pale yellow granules. Mp 96–97 °C ($Et_2O$–hexane). IR (KBr): 2163, 1729, 1249, 1142, 851 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$0.22 (s, 9H), 3.78 (s, 3H), 6.41 (d, $J$ = 3.4 Hz, 1H), 7.50–7.57 (m, 2H), 7.59 (d, $J$ = 3.4 Hz, 1H), 7.60–7.66 (m, 1H), 7.93–7.98 (m, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ –0.2, 51.8, 97.0, 100.8, 114.7, 117.1, 127.1, 127.2, 128.0, 128.9, 134.0, 138.7, 159.1. Anal. Calcd for $C_{17}H_{19}NO_4SSi$: C, 56.48; H, 5.30; N, 3.87. Found: C, 56.48; H, 5.11; N, 3.85.

**Typical procedure for Sonogashira–Hagihara cross-coupling of methyl *N*-benzenesulfonyl-3-bromo-1*H*-pyrrole-2-carboxylate (2) with terminal alkynes 5 (Table 2).** Under an argon atmosphere, a mixture of methyl *N*-benzenesulfonyl-3-bromo-1*H*-pyrrole-2-carboxylate (**2**) (344 mg, 1.00 mmol), an appropriate terminal alkyne **5** (2.40 mmol), CuI (3.8 mg, 20 μmol), $Pd(PPh_3)_2Cl_2$ (7.0 mg, 10 μmol), and $Et_3N$ (1.0 mL) was heated in a sealed tube at 80 °C for 20 h. After cooling to rt, the mixture was diluted with $CH_2Cl_2$ and evaporated. The residue was diluted with $CH_2Cl_2$ and the mixture was washed with water and brine, dried over $Na_2SO_4$, and evaporated. The residue was purified by column chromatography over silica gel 60N to give **4**. The results are summarized in Table 2.

**Methyl *N*-(benzenesulfonyl)-3-(2-phenylethynyl)-1*H*-pyrrole-2-carboxylate (4b).** According to the typical procedure, phenylacetylene (**5b**) (264 μL, 2.40 mmol) was reacted. After purification by flash chromatography over silica gel 60N (hexane–EtOAc = 7:1), **4b** was obtained as a pale brown solid (346 mg, 95%). Recrystallization from $Et_2O$–hexane gave pale brown needles. Mp 110–112 °C. IR (KBr): 1720, 1365, 1246, 1140 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 3.83 (s, 3H), 6.48 (d, $J$ = 3.4 Hz, 1H), 7.31–7.36 (m, 3H), 7.45–7.50 (m, 2H), 7.52–7.58 (m, 2H), 7.61–7.67 (m, 1H), 7.65 (d, $J$ = 3.4 Hz,

1H), 7.96–8.00 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 52.0, 82.1, 94.9, 114.5, 117.5, 122.9, 126.3, 127.5, 128.0, 128.4, 128.7, 128.9, 131.6, 134.0, 138.7, 159.2. Anal. Calcd for $C_{20}H_{15}NO_4S$: C, 65.74; H, 4.14; N, 3.83. Found: C, 65.65; H, 3.94; N, 3.82.

**Methyl *N*-(benzenesulfonyl)-3-[2-(cyclohex-1-en-1yl)ethynyl]-1*H*-pyrrole-2-carboxylate (4c).** According to the typical procedure, 1-ethynylcyclohexene (**5c**) (282 μL, 2.40 mmol) was reacted. After chromatographic purification over silica gel 60N (hexane–toluene = 2:1 to toluene), **4c** was obtained as a pale brown solid (120 mg, 33%). Recrystallization from $Et_2O$–hexane gave a pale brown powder. Mp 75.5–79 °C. IR (KBr): 2209, 1723, 1375, 1240, 1140 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.55–1.70 (m, 4H), 2.09–2.21 (m, 4H), 3.78 (s, 3H), 6.17–6.22 (m, 1H), 6.38 (d, $J$ = 3.4 Hz, 1H), 7.50–7.56 (m, 2H), 7.60 (d, $J$ = 3.4 Hz, 1H), 7.60–7.66 (m, 1H), 7.92–7.96 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 21.4, 22.2, 25.8, 29.0, 51.8, 79.5, 97.1, 114.5, 118.2, 120.6, 125.8, 127.5, 127.9, 128.9, 133.9, 136.2, 138.9, 159.3. Anal. Calcd for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79. Found: C, 64.77; H, 5.38; N, 3.55.

**Methyl *N*-(benzenesulfonyl)-3-(hex-1-yn-1-yl)-1*H*-pyrrole-2-carboxylate (4d).** According to the typical procedure, 1-hexyne (**5d**) (276 μL, 2.40 mmol) was reacted. After purification by flash chromatography over silica gel 60N (hexane–EtOAc = 4:1), **4d** was obtained as a pale brown solid (161 mg, 47%). Recrystallization from $Et_2O$–hexane gave colorless plates. Mp 62.5–63.5 °C. IR (KBr): 2234, 1717, 1444, 1249, 1174, 1136 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 0.92 (t, $J$ = 7.3 Hz, 3H), 1.41–1.50 (m, 2H), 1.52–1.58 (m, 2H), 2.41 (t, $J$ = 7.0 Hz, 2H), 3.77 (s, 3H), 6.35 (d, $J$ = 3.4 Hz, 1H), 7.51–7.56 (m, 2H), 7.58 (d, $J$ = 3.4 Hz, 1H), 7.60–7.65 (m, 1H), 7.92–7.96 (m, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ 13.6, 19.3, 21.8, 30.6, 51.8, 73.1, 96.7, 114.8, 118.3, 126.0, 127.2, 127.9, 128.9, 133.9, 138.9, 159.4. HRMS (*m/z*) Calcd for $C_{18}H_{20}NO_4S$ [$(M+H)^+$]: 346.1113. Found: 346.1113.

**Methyl *N*-(benzenesulfonyl)-3-{3-[(triisopropylsilyl)oxy]prop-1-yn-1-yl}-1*H*-pyrrole-2-carboxylate (4e).** According to the typical procedure, triisopropyl(prop-2-yn-1-yloxy)silane (**5e**)[21] (510 mg, 2.40 mmol) was reacted. After chromatographic purification over silica gel 60N (hexane–EtOAc = 10:1), **4e** was obtained as a pale brown solid (265 mg, 56%). Recrystallization from $Et_2O$–hexane gave pale yellow plates. Mp 80–81 °C. IR (KBr): 1725, 1243, 1136, 1087, 1057 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.04–1.19 (m, 21H), 3.77 (s, 3H), 4.58 (s, 2H), 6.38 (d, $J$ = 3.4 Hz, 1H), 7.51–7.57 (m, 2H), 7.59 (d, $J$ = 3.4 Hz, 1H), 7.61–7.67 (m, 1H), 7.94–7.98 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 12.0, 17.9, 52.0, 52.5, 77.0, 93.7, 114.8, 117.0, 126.4, 127.1, 128.0, 128.9, 134.0, 138.8, 159.3. HRMS (*m/z*) Calcd for $C_{24}H_{34}NO_5SSi$ [$(M+H)^+$]: 476.1927. Found: 476.1928.

**Methyl 3-bromo-1*H*-pyrrole-2-carboxylate (7).** $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 3.90 (s, 3H), 6.35 (t, $J$ = 2.9 Hz, 1H), 6.88 (t, $J$ = 2.9 Hz, 1H), 9.31 (br s, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ 51.7, 103.6, 114.9, 120.1, 122.6, 160.6. These physical and spectroscopic data are in good agreement with those previously reported.[22]

**Typical procedure for iodine-mediated cyclization of 3-alkynylated pyrrole-2-carboxylate 4 (Table 3).** Under an argon atmosphere, a mixture of 3-alkynylated pyrrole-2-carboxylate **4** (0.277 mmol), $I_2$ (84.2 mg, 0.332 mmol), and $CH_2Cl_2$ (2.0 mL) was stirred in a sealed tube for 18 h at 30 °C. After addition of 10% aqueous $Na_2SO_3$, the products were extracted with $CH_2Cl_2$ and the extract was washed with water and brine, dried over $Na_2SO_4$, and evaporated. The residue was purified by column chromatography over silica gel 60N to give **3**. The results are summarized in Table 3.

**1-(Benzenesulfonyl)-4-iodo-5-phenylpyrano[3,4-*b*]pyrrol-7(1*H*)-one (3b).** According to the typical procedure, methyl *N*-(benzenesulfonyl)-3-(2-phenylethynyl)-1*H*-pyrrole-2-carboxylate (**4b**) (102 mg, 0.277 mmol) was reacted. After chromatographic purification over silica gel 60N (hexane–EtOAc = 3:1), **3b** was obtained as a pale brown solid (127 mg, 96%). Recrystallization from $CH_2Cl_2$–hexane gave colorless needles. Mp 144.5–145.5 °C. IR (KBr): 1728, 1390, 1178, 1143, 1037 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 6.56 (d, $J$ = 3.4 Hz, 1H), 7.39–7.46 (m, 3H), 7.53–7.57 (m, 2H), 7.63–7.68 (m, 3H), 8.00 (d, $J$ = 3.4 Hz, 1H), 8.16–8.20 (m, 2H). $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 65.2, 111.4, 114.8, 128.1, 129.1, 129.2, 129.7, 130.2, 131.8, 133.5, 134.7, 137.4, 142.3, 152.2, 155.8. HRMS (*m/z*) Calcd for $C_{19}H_{13}INO_4S$ [$(M+H)^+$]: 477.9610. Found: 477.9637.

**1-(Benzenesulfonyl)-5-(cyclohex-1-en-1-yl)-4-iodopyrano[3,4-*b*]pyrrol-7(1*H*)-one (3c).** According to the typical procedure, methyl *N*-(benzenesulfonyl)-3-[2-(cyclohex-1-en-1yl)ethynyl]-1*H*-pyrrole-2-carboxylate (**4c**) (51.1 mg, 0.138 mmol) was reacted. After chromatographic purification over silica gel 60N (toluene), **3c** was obtained as a colorless oil (62.1 mg, 93%). IR (KBr): 1751, 1383, 1176, 1141, 1034 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 1.60–1.67 (m, 2H), 1.67–1.74 (m, 2H), 2.15–2.21 (m, 2H), 2.22–2.27 (m, 2H), 6.14–6.18 (m, 1H), 6.47 (d, $J$ = 3.4 Hz, 1H), 7.51–7.56 (m, 2H), 7.62–7.66 (m, 1H), 7.94 (d, $J$ = 3.4 Hz, 1H), 8.14–8.17 (m, 2H). $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 21.5, 22.2, 25.1, 26.3, 63.7, 111.3, 114.6, 129.1, 129.1, 131.5, 132.2, 134.6, 135.3, 137.5, 142.3, 152.4, 158.5. HRMS (*m/z*) Calcd for $C_{19}H_{17}INO_4S$ [$(M+H)^+$]: 481.9923. Found: 481.9907.

**1-(Benzenesulfonyl)-5-butyl-4-iodopyrano[3,4-*b*]pyrrol-7(1*H*)-one (3d).** According to the typical procedure, methyl *N*-(benzenesulfonyl)-3-(hex-1-yn-1-yl)-1*H*-pyrrole-2-carboxylate (**4d**) (66.5 mg, 0.193 mmol) was reacted. After chromatographic purification over silica gel 60N (hexane–EtOAc = 5:1), **3d** was obtained as a colorless oil (81.3 mg, 92%). IR (KBr): 1745, 1382, 1175, 1141, 1034 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 0.92 (t, $J$ = 7.4 Hz, 3H), 1.32–1.41 (m, 2H), 1.58–1.66 (m, 2H), 2.74 (t, $J$ = 7.7 Hz, 2H), 6.41 (d, $J$ = 3.4 Hz, 1H), 7.51–7.56 (m, 2H), 7.62–7.67 (m, 1H), 7.93 (d, $J$ = 3.4 Hz, 1H), 8.13–8.17 (m, 2H). $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 13.7, 22.1, 29.4, 35.2, 65.5, 110.4, 114.5, 129.1, 129.1, 131.7, 134.6, 137.5, 141.8, 152.7, 159.8. HRMS (*m/z*) Calcd for $C_{17}H_{17}INO_4S$ [$(M+H)^+$]: 457.9923. Found: 457.9926.

**1-(Benzenesulfonyl)-4-iodo-5-{[(triisopropylsilyl)oxy]methyl}pyrano[3,4-*b*]pyrrol-7(1*H*)-one (3e).** According to the typical procedure, methyl *N*-(benzenesulfonyl)-3-{3-[(triisopropylsilyl)oxy]-prop-1-yn-1-yl}-1*H*-pyrrole-2-carboxylate (**4e**) (132 mg, 0.277 mmol) was reacted. After chromatographic purification over silica gel 60N (hexane–EtOAc = 5:1), **3e** was obtained as a colorless solid (120 mg, 74%). Recrystallization from $Et_2O$–hexane gave colorless plates. Mp 138.5–139.5 °C. IR (KBr): 1745, 1383, 1176, 1140, 1040 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 1.05–1.09 (m, 18H), 1.10–1.20 (m, 3H), 4.73 (s, 2H), 6.47 (d, $J$ = 3.4 Hz, 1H), 7.51–7.56 (m, 2H), 7.62–7.67 (m, 1H), 7.96 (d, $J$ = 3.4 Hz, 1H), 8.13–8.17 (m, 2H). $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 12.0, 17.9, 64.6, 66.5, 110.6, 115.4, 129.1, 129.2, 131.7, 134.7, 137.4, 141.2, 152.2, 156.0. HRMS (*m/z*) Calcd for $C_{23}H_{31}INO_5SSi$ [$(M+H)^+$]: 588.0737. Found: 588.0732.

**1-(Benzenesulfonyl)-4-iodo-5-(trimethylsilyl)pyrano[3,4-*b*]pyrrol-7(1*H*)-one (3a).** According to the typical procedure, methyl *N*-(benzenesulfonyl)-3-[2-(trimethylsilyl)ethynyl]-1*H*-pyrrole-2-carboxylate (**4a**) (100 mg, 0.277 mmol) was reacted for 120 h. After chromatographic purification over silica gel 60N (toluene to toluene–EtOAc = 10:1), **3a** was obtained as a colorless oil (104 mg, 79%). IR (KBr): 1743, 1383, 1203, 1029, 847 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 0.41 (s, 9H), 6.43 (d, $J$ = 3.4 Hz, 1H), 7.51–7.56 (m, 2H), 7.62–7.66 (m, 1H), 7.95 (d, $J$ = 3.4 Hz, 1H), 8.14–8.18 (m, 2H). $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ –1.1, 77.4, 110.1, 116.3, 129.1, 129.2, 131.0, 134.6, 137.5, 140.2, 154.0, 166.1. HRMS (*m/z*) Calcd for $C_{16}H_{17}INO_4SSi$ [$(M+H)^+$]: 473.9692. Found: 473.9683.

**1-(Benzenesulfonyl)-4-(4-methoxyphenyl)-5-phenylpyrano[3,4-*b*]pyrrol-7(1*H*)-one (1a).** Under an argon atmosphere, a mixture of 1-(benzenesulfonyl)-4-iodo-5-phenylpyrano[3,4-*b*]pyrrol-7(1*H*)-one (**3b**) (40.0 mg, 83.8 μmol), 4-methoxyphenylboronic acid (**8**) (25.5 mg, 0.168 mmol), $Pd(PPh_3)_4$ (9.7 mg, 8.4 μmol), $Na_2CO_3$ (58.6 mg, 0.553 mmol), DME (3.0 mL), and degassed water (0.3 mL) was heated in a sealed tube at 85 °C for 24 h. After cooling to rt, the solvent was evaporated *in vacuo* and the residue was extracted with $CH_2Cl_2$. The extract was washed with water and brine, dried over $Na_2SO_4$, and evaporated. The residue was purified by flash chromatography over silica gel 60N (hexane–EtOAc = 3:1) to give **1a** as a colorless semisolid (20.4 mg, 53%). Recrystallization from $Et_2O$–hexane gave pale yellow granules. Mp 169.5–170.5 °C. IR (KBr): 1731, 1514, 1375, 1248, 1177 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 3.83 (s, 3H), 6.28 (d, $J$ = 3.4 Hz, 1H), 6.87–6.91 (m, 2H), 7.10–7.14 (m, 2H), 7.16–7.20 (m, 2H), 7.21–7.25 (m, 1H), 7.27–7.31 (m, 2H), 7.53–7.58 (m, 2H), 7.63–7.68 (m, 1H), 7.92 (d, $J$ = 3.4 Hz, 1H), 8.20–8.24 (m, 2H). $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 55.3, 106.9, 113.7, 114.5, 116.2, 126.1, 128.0, 129.0, 129.1, 129.1, 129.1, 131.2, 132.1, 132.4, 134.5, 137.8, 141.0, 152.4, 152.7, 159.4. HRMS (*m/z*) Calcd for $C_{26}H_{20}NO_5S$ [$(M+H)^+$]: 458.1062. Found: 458.1065.

**1-(Benzenesulfonyl)-4-[2-(4-methoxyphenyl)ethynyl]-5-phenylpyrano[3,4-*b*]pyrrol-7(1*H*)-one (1b).** Under an argon atmosphere, a mixture of 1-(benzenesulfonyl)-4-iodo-5-phenylpyrano[3,4-*b*]pyrrol-

7(1*H*)-one (**3b**) (40.0 mg, 83.8 μmol), 4-ethynylanisole (**9**) (26.1 μL, 0.201 mmol), CuI (0.32 mg, 1.7 μmol), $Pd(PPh_3)_2Cl_2$ (0.59 mg, 0.84 μmol), and $Et_3N$ (1.0 mL) was heated in a sealed tube at 80 °C for 24 h. After cooling to rt, the mixture was diluted with $CH_2Cl_2$ and evaporated. The residue was diluted with $CH_2Cl_2$ and the mixture was washed with water and brine, dried over $Na_2SO_4$, and evaporated. The residue was purified by flash chromatography over silica gel 60N (hexane–EtOAc = 3:1) to give **1b** as a pale yellow solid (38.3 mg, 95%). Recrystallization from $CH_2Cl_2$–hexane gave pale yellow plates. Mp 201.5–202.5 °C. IR (KBr): 1736, 1512, 1384, 1253, 1175 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 3.84 (s, 3H), 6.76 (d, $J$ = 3.4 Hz, 1H), 6.87–6.91 (m, 2H), 7.40–7.47 (m, 5H), 7.53–7.58 (m, 2H), 7.63–7.67 (m, 1H), 8.00 (d, $J$ = 3.4 Hz, 1H), 8.13–8.17 (m, 2H), 8.17–8.21 (m, 2H). $^{13}C$ NMR (126 MHz, $CDCl_3$): $\delta$ 55.4, 80.7, 96.7, 96.9, 107.1, 114.2, 114.6, 115.4, 128.1, 128.2, 129.0, 129.2, 130.3, 131.9, 132.5, 132.9, 134.6, 137.6, 140.0, 151.6, 157.4, 160.1. HRMS (*m/z*) Calcd for $C_{28}H_{20}NO_5S$ [$(M+H)^+$]: 482.1062. Found: 482.1060.

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