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Gold-silver catalyzed straightforward one pot synthesis of pyrano[3,4-*b*]pyrrol-7(1*H*)-ones.

P.-O. Delaye,[a] J. Petrignet,[a] E. Thiery[a] and J. Thibonnet[a*]

Pyrano[3,4-*b*]pyrrol-7(1*H*)-one is a bicyclic structure that is rarely described in the literature but found in numerous polycyclic natural products as Lamellarins. This work presents an one-pot synthesis of pyrano[3,4-*b*]pyrrol-7(1*H*)-one substituted in 2- and 5-position. The reaction proceeds *via* a one-pot two steps *5-endo*-dig and *6-endo*-dig cyclizations catalyzed by a cationic gold complex with high regioselectivity

Introduction

Pyrano[3,4-*b*]pyrrol-7(1*H*)-one is a bicyclic structure found in many polyheterocyclic molecules and natural compounds as Ningalin B and Lamellarins (Figure 1). Ningalin B is a marine natural product, and its are potent multidrug resistance reversal agents of cancer cells.[1] Pentacyclic Lamellarin D is one of the first example of Lamellarins alkaloids isolated from various marine organisms such as mollusks, sponges and ascidians.[2,3] Since their discovery in 1985, about 50 new Lamellarins have been isolated and interest in these molecules has been growing due to their cytotoxicity and antitumor activity, multidrugs resistance reversal activity, HIV-1 integrase inhibition, and immunomodulatory activity.[4] Due to their various biological properties and the difficulty in obtaining large quantities of natural resources, many total syntheses of various Lamellarins have been published in the last decade.[3,5] The preparation of analogs of these alkaloids has also been studied as an issue for pharmaco-modulating the Lamellarin core[6] and for designing structures that are easier to access. Thus, diversely substituted molecules with tricyclic chromeno[3,4-*b*]-pyrrol-4(3*H*)-one[7] and chromeno[3,4-*b*]-indol-6(7*H*)-one[8] scaffold were prepared. The latter showed inhibitory activities of DYRK1A kinase. However, the bicyclic pyrano[3,4-*b*]pyrrol-7(1*H*)-one is rarely described in the literature, and to the best of our knowledge, only few examples have been reported.[9] Indeed, most recent works proposed an access to those structures starting from 1-methypyrrole-2-carboxylic acid, pyranone ring being formed by annulation with alkynes in presence of ruthenium or rhodium catalysts. [9b,c] Herein, the development of a new synthetic pathway to access both pyrrole and pyranone cycles in a one-pot process is highly challenging.

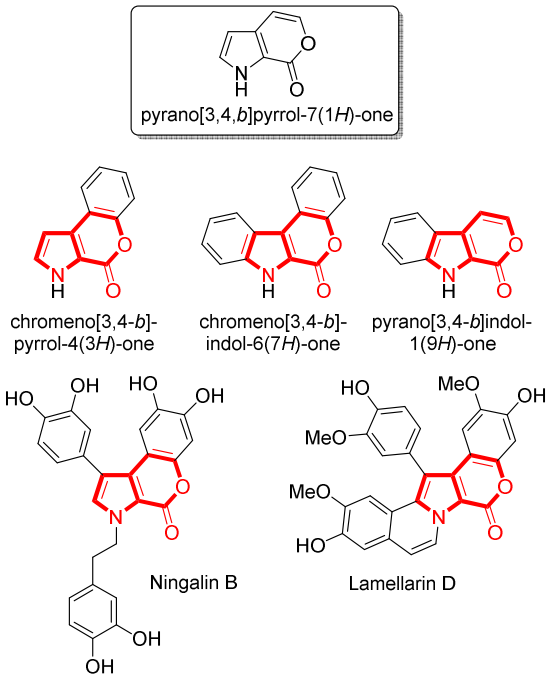


Figure 1.

Over the past ten years, our group has been developing methodologies based on electrophilic or transition metal-catalyzed cyclization. We reported various approaches for the synthesis of biologically interesting heterocycles,[10] such as tricyclic pyrano[3,4-*b*]indol-1(9H)-ones synthetized by a copper (I) catalyzed domino reaction.[10d] The strategy we envision here for the preparation of pyrano[3,4-*b*]pyrrol-7(*1H*)-ones **3** is based on a double alkyne activation of diynes **2** (Figure 2), catalyzed by platinum[11] or gold[12] salts as known for their remarkable activation of alkynes.[13] The compound **3** could be formed *via* heterocycle rings formed through *5-endo*-dig and *6-endo*-dig cyclization modes. The latter competes with the *5-exo* mode—the regioselectivity is known to be dependent on the chain length, the substitution pattern on the chain, and the metal transition.[14] The diynes **2** can be prepared *via* double Sonogashira cross coupling from β,β-dibromodehydroalanine derivatives **1** (Figure 2).

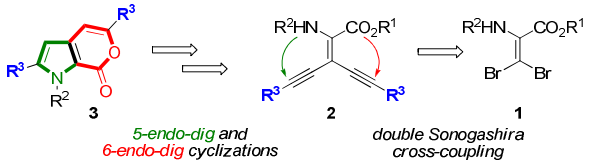
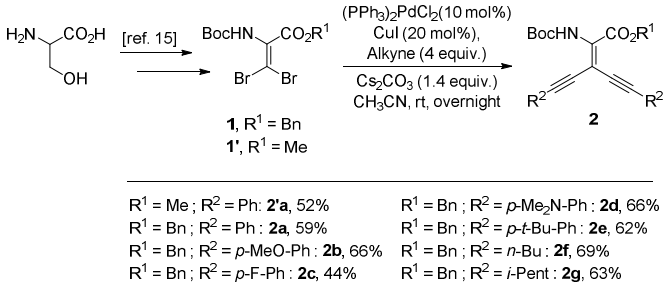


Figure 2. Retrosynthetic pathways for the synthesis of pyrano[3,4-*b*]pyrrol-7(1*H*)-ones.

Results and **discussion**

First, β,β-dibromodehydroalanine derivatives **1** and **1'** were prepared according to procedures previously described in the literature[15] (four steps from Serine (Scheme 1)). Compounds **2** were then prepared in average to good yields using a double Sonogashira cross coupling between compounds **1** and various alkynes using a procedure modified from the literature.[15c] Derivative of compound **1** were prepared by replacing *tert*-butoxycarbonyl group by benzyloxycarbonyl group. Unfortunately, we did not succeed in carrying out the double Sonogashira coupling with such a protective group. Mono coupling debrominated product was obtained.



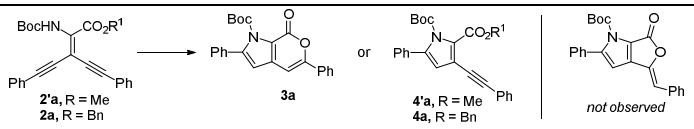
R^1 = Me ; R^2 = Ph: **2'a**, 52%	R^1 = Bn ; R^2 = *p*-Me_2N-Ph : **2d**, 66%
R^1 = Bn ; R^2 = Ph : **2a**, 59%	R^1 = Bn ; R^2 = *p*-*t*-Bu-Ph : **2e**, 62%
R^1 = Bn ; R^2 = *p*-MeO-Ph : **2b**, 66%	R^1 = Bn ; R^2 = *n*-Bu : **2f**, 69%
R^1 = Bn ; R^2 = *p*-F-Ph : **2c**, 44%	R^1 = Bn ; R^2 = *i*-Pent : **2g**, 63%

Scheme 1. Synthesis of compounds **2**.

We investigated the use of platinum (II) and (IV) salts in toluene for the cyclization of compounds **2'a** (Table 1, entries 1 and 2) and **2a** (entries 3 and 4). In all cases, we observed only the sole nitrogen cyclization *via 5-endo-dig* pathway that leads to pyrroles **4'a** and **4a** with good yields. We then considered the use of gold (I) salts associated with silver salts in order to facilitate the formation of cationic gold. Compound **2'a** in the presence of (triphenylphosphine)gold (I) chloride and silver tetrafluoroborate in dichloromethane at 50 °C, leads to pyrrole **4'a** (entry 5). According to the conditions described by Asao *et al.,* we used *tert*-butanol as an additive to promote the living of R^1 group of the ester and formation of the lactone ring.[16] The addition of *t*-BuOH to the reaction mixture lead to a loss of reactivity (conversion = 50%) and an inseparable mixture of **3a** and **4'a** in proportions of 40:60 (entry 6). On the other hand, under the same conditions, substrate **2a** will form the compound **3a** with no trace of formation of the pyrrole **4a** in the crude product and in modest yield (52%; entry 7). The pyrano[3,4-b] pyrrol-7(1H)-one structure of compound **3a** was determined by NMR experiments (see SI-S15). We thus confirmed the regioselectivity of the *6-endo*-dig cyclization between the alkyne and the ester. The cyclization product from *5-exo*-dig cyclisation was never observed.The amounts of catalysts (entries 8) and the solvent (entries 8-10) are then optimized from **2a**. The use of gold salts as catalysts and silver salts as co-catalysts are required. Indeed, there is no conversion without silver salts (entry 11). Without gold catalyst, the conversion is not complete, and a mixture of **3a**, **4'a,** and a third indeterminate compound was obtained (entry 12). The products could not be separated. The use of silver triflate instead of silver tetrafluoroborate allows the formation of **3a** in similar yields.

We then prepared a series of bicyclic compounds with our method using gold catalysis (Table 2). The preparation of these compounds also appeared including aryls (entries 1-3 and 5) and alkyls (entries 6 and 7) with yields of up to 82%. Here we also noted less efficient cyclization with electron-poor aryls (entry 3). This result can be explained by the fact that the position attacked on the alkyne moiety was less electrophilic due to the electron-poor substituent. The efficiency of gold was reduced by the amino substituted aryl. This resulted in the only example without closing of both cycles (entry 4). In this case, pyrrole **4d** was the only product.

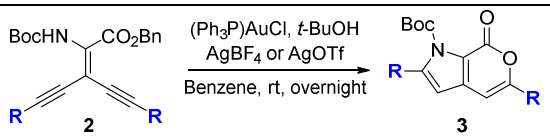
Table 1. Optimization of reaction conditions[a]

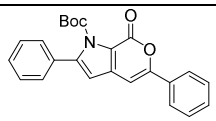
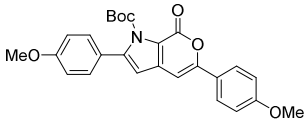
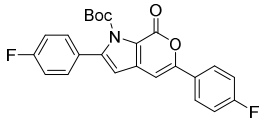
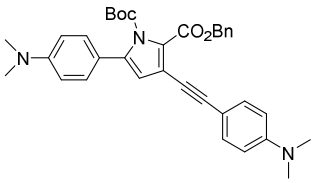
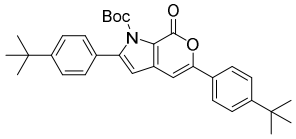
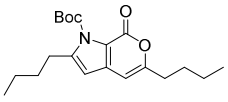
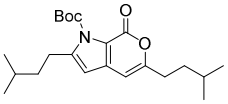


Entry	Substrate	Catalysts	Additive	Conditions	3[b]	4[b]
1	**2'a**	$PtCl_4$, 5 mol%	-	Toluene, 90°C, overnight	-	**4'a**, 64 %
2	**2'a**	$PtCl_2$, 5 mol%	-	Toluene, 90°C, overnight	-	**4'a**, 84 %
3	**2a**	$PtCl_2$, 5 mol%	-	Toluene, 90°C, overnight	-	**4a**, 70 %
4	**2a**	$PtCl_2$, 5 mol%	-	Toluene, 75°C, overnight	-	**4a**, 70 %
5	**2'a**	PPh_3AuCl, 5 mol%, $AgBF_4$, 6 mol%	-	CH_2Cl_2, 50°C, 24 h	-	**4'a**, 52 %
6	**2'a**	PPh_3AuCl, 5 mol%, $AgBF_4$, 5 mol%	*t*-BuOH (3 equiv.)	Benzene, rt, overnight	nd[c]	nd[c]
7	**2a**	PPh_3AuCl, 5 mol%, $AgBF_4$, 5 mol%	*t*-BuOH (3 equiv.)	Benzene, rt, overnight	**3a**, 52 %	-
8	**2a**	PPh_3AuCl, 10 mol%, $AgBF_4$, 10 mol%	*t*-BuOH (3 equiv.)	Benzene, rt, overnight	**3a**, 72 %	-
9	**2a**	PPh_3AuCl, 10 mol%, $AgBF_4$, 10 mol%	*t*-BuOH (3 equiv.)	Toluene, rt, overnight	**3a**, 60 %	-
10	**2a**	PPh_3AuCl, 10 mol%, $AgBF_4$, 10 mol%	*t*-BuOH (3 equiv.)	CH_2Cl_2, rt, overnight	**3a**, 41 %	-
11	**2a**	PPh_3AuCl, 5 mol%,	*t*-BuOH (3equiv.)	Toluene, rt, overnight	-	-
12	**2a**	$AgBF_4$, 10 mol%	*t*-BuOH (3 equiv.)	Benzene, rt, overnight	nd[c]	nd[c]

[a] Reactions were typically performed with 0.5 mmol of substrate. [b] Isolated yield. [c] Inseparable mixture

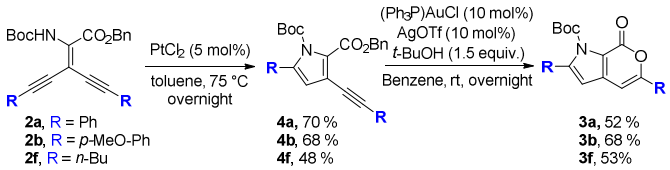
Table 2. Synthesis of pyrano[3,4-*b*]pyrrol-7(1*H*)-ones **3**.[a]



Entry	**2**	Products	Yield (%)[b]
1	**2a**		**3a**, 72%
2	**2b**		**3b**, 82%
3	**2c**		**3c**, 45%
4	**2d**		**4d**, 58%
5	**2e**		**3e**, 72%
6	**2f**		**3f**, 66%
7	**2g**		**3g**, 75%

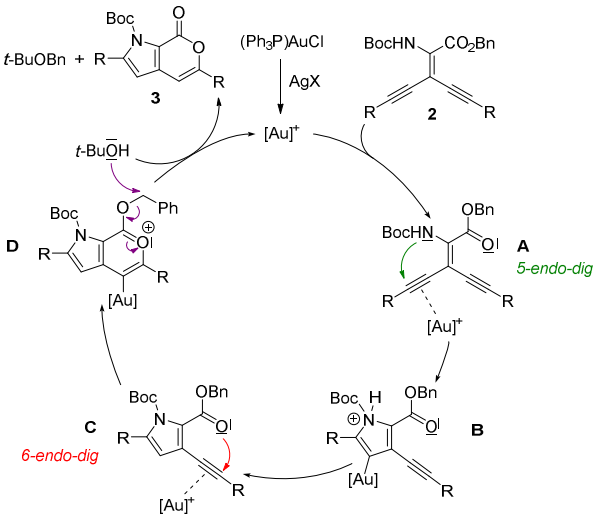
[a] Conditions: **2** (0.5 mmol), $(Ph_3P)AuCl$ (0.05 mmol), $AgBF_4$ or AgOTf (0.05 mmol), *t*-BuOH (1.5 mmol), benzene (2 mL), rt, overnight. [b] Isolated yields.

Of note, the synthesis of compounds **3** can be accomplished in a two steps sequences because platinum (II) chloride allowed selective pyrrole synthesis. Trisubstituted pyrroles **4** were synthesized from **2a** in the presence of platinum (II) chloride in toluene at 75 °C (Scheme 2). These compounds, in the presence of gold (I) and silver (I) salts, led to the formation of pyrano[3,4-*b*]pyrrol-7(1*H*)-ones **3** according to a *6-exo-dig* cyclization. Note that the yields are lower than those obtained by the one-pot procedure (Table 2).



Scheme 2. Synthesis of compounds **3** in two steps.

According to our results and the literature, we propose a mechanism based on gold catalysis (Scheme 3). First, silver (I) will make it possible to form cationic gold (I), which interacts with the π-system of the substrate to form intermediate **A**. The nucleophilic attack of the nitrogen then proceeds *via 5-endo-dig* cyclization to form the vinylgold species **B**. The protodemetallation of **B** liberated the pyrrole compound and the gold catalyst, which can then interact with the second alkyne to form the intermediate **C**. The nucleophilic attack of oxygen, according to a *6-endo-dig* cyclization, leads to organogold **D**, which liberates compound **3** and gold (I) catalyst by protodemetallation.



Scheme 3. Proposed reaction mechanism.

Conclusions

In summary, we developed a gold-catalyzed synthesis of pyrano[3,4-*b*]pyrrol-7(1*H*)-one derivatives from benzyl β,β-diacetylenic dehydroalanine esters. The substrates can be easily prepared by Sonogashira coupling, and this reaction offers two-step and rapid access to various new pyrano-pyrroles resulting from double intramolecular nucleophilic *5-endo* and *6-endo*-additions to a carbon-carbon triple bond. We are currently evaluating these compounds for their biological effects. Moreover, studies to extend the scope of the synthetic utility of this one-pot reaction are underway in our laboratory.

Experimental

All reactions were carried out under argon atmosphere in dried glassware. Toluene and benzene were dried and freshly distilled from sodium. Acetonitrile was dried and freshly distilled from CaH_2. $(Ph_3P)AuCl$, AgOTf, $AgBF_4$ and CuI were purchased from Sigma-Aldrich®, in ≥99.9%, ≥99.95% and 98% purity respectively. $(Ph_3P)_2PdCl_2$ was prepared from $PdCl_2$ and PPh_3. Reactions were monitored by TLC with Merck® Silica gel 60 F_{254}. Purifications by flash chromatography were carried out using Merck® Geduran® Si 60 silica gel (40-63 µm). ^1H NMR spectra were recorded on a Bruker® Avance 300 (300 MHz) NMR spectrometer, using $CDCl_3$ as solvent. Data, reported using Me_4Si (δ_H = 0.00 ppm) as internal reference, were as follows (in order): chemical shift (δ in ppm relative to Me_4Si), multiplicity (s, d, t, q, m, br for singlet,

doublet, triplet, quartet, multiplet, broad) and coupling constants (*J* in Hz). ^{13}C NMR was recorded at 75 MHz on the same instrument, using the $CDCl_3$ solvent peak at (δ_C = 77.16 ppm) as reference. ^{19}F NMR was recorded at 282 MHz on the same instrument, using the $CClF_3$ peak at (δ_F = 0.0 ppm) as internal reference. Mass spectra were obtained on a Hewlett Packard (engine 5988A) by direct inlet at 70eV. IR spectra were recorded on a Perkin-Elmer Spectrum One spectrophotometer. Melting points were uncorrected.

Preparation of starting materials

Compound **2'** was prepared by the reported procedure.[15c]

Preparation of compounds **1**, **2a-g** is reported in the supporting information.

General procedure for the synthesis of compounds (3)

$AgBF_4$ (10 mol%, 0.05 mmol, 10 mg) or AgOTf (10 mol%, 0.05 mmol, 13 mg) was added to a solution of (Ph_3P)AuCl (10 mol%, 0.05 mmol, 25 mg) in freshly distilled benzene (2 mL). After 2 minutes, **2** (0.5 mml) was added, followed by *t*-BuOH (3 equiv., 1.5 mmol, 138 µL). The reaction was then stirred overnight at room temperature before it was filtered through a pad of celite with EtOAc. The filtrate was then washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$ and solvents were evaporated under vacuum. Residues were purified by flash chromatography on silica gel to give compounds **3**.

***tert*-Butyl-7-oxo-2,5-diphenylpyrano[3,4-*b*]pyrrole-1(7*H*)-carboxylate (3a):** Eluant: PE/Et_2O 80/20, yield = 72%; $C_{24}H_{21}NO_4$; Rf (PE/AcOEt : 90/10) = 0.30 ; yellow solid; m.p.: 135-137 °C , IR (ATR): ν = 2979, 2928, 1761, 1727, 1285, 1259, 1146, 1124, 690; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.54 (s, 9H), 6.40 (s, 1H), 6.97 (s, 1H), 7.26-7.51 (m, 8H), 7.84-7.87 (m, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.3 (CH_3), 86.4 (Cq), 97.5 (CH), 106.5 (CH), 117.7 (Cq), 125.2 (CH), 128.5 (CH), 128.6 (CH), 128.8 (CH), 129.2 (CH), 129.5 (CH), 131.1 (Cq), 132.4 (Cq), 134.4 (Cq), 144.6 (Cq), 148.4 (Cq), 153.9 (Cq), 154.6 (Cq) ; HRMS (ESI) calcd. for $C_{24}H_{22}NO_4$ [M+H]+: 388.15433; found: 388.15441.

***tert*-Butyl-2,5-bis(4-methoxyphenyl)-7-oxopyrano[3,4-*b*]pyrrole-1(7*H*)-carboxylate (3b):** Eluant: PE/AcOEt 70/30, yield = 82%; $C_{26}H_{25}NO_6$; Rf (PE/Et_2O: 70/30) = 0.16 ; yellow solid; m.p.: 131-133 °C; IR (ATR): *ν* = 2941, 2842, 1748, 1724, 1608, 1291, 1249, 1025, 817; ^1H NMR (300 MHz, $CDCl_3$): *δ* = 1.57 (s, 9H), 3.85 (s, 3H), 3.86 (s, 3H), 6.31 (s, 1H), 6.83 (s, 1H), 6.94-9.98 (m, 4H), 7.42 (m, 2H), 7.79 (m, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 27.5 (CH_3), 55.49 (CH_3), 55.52 (CH_3), 86.3 (Cq), 96.0 (CH), 106.0 (CH), 114.0 (CH), 114.3 (CH), 123.5 (Cq),125.3 (Cq), 126.8 (CH), 130.2 (CH), 135.0 (Cq), 144.8 (Cq), 148.7 (Cq), 154.1 (Cq), 154.9 (Cq), 160.5 (Cq), 160.8 (Cq); HRMS (ESI) calcd. for $C_{26}H_{26}NO_6$ $[M+H]^+$: 448.17546; found: 448.17540.

***tert*-Butyl-2,5-bis(4-fluorophenyl)-7-oxopyrano[3,4-*b*]pyrrole-1(7*H*)-carboxylate (3c):** Eluant: PE/AcOEt 80/20, yield = 45%; $C_{24}H_{19}F_2NO_4$; Rf (PE/Et_2O: 80/20) = 0.27; yellow solid; m.p.: 138-140 °C IR (ATR): *ν* = 3078, 2985, 2933, 1762, 1731, 1291, 1156, 1141, 1125, 828; ^1H NMR (300 MHz, $CDCl_3$): *δ* = 1.54 (s, 9H), 6.36 (s, 1H), 6.88 (s, 1H), 7.09-7.17 (m, 4H), 7.44-7.49 (m, 2H), 7.80-7.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 27.4 (CH_3), 86.7 (Cq), 97.2 (CH), 106.7 (CH), 115.7 (d, $^2J_{C-F}$ = 21.9 Hz, CH), 116.0 (d, $^2J_{C-F}$ = 22.0 Hz, CH), 117.6 (Cq), 127.2 (d, $^4J_{C-F}$ = 3.4 Hz, Cq), 127.3 (d, $^3J_{C-F}$ = 8.3 Hz, CH), 128.7 (d, $^4J_{C-F}$ = 3.2 Hz, Cq), 130.8 (d, $^3J_{C-F}$ = 8.4 Hz, CH), 134.4 (Cq), 143.8 (Cq), 148.3 (Cq), 153.7 (Cq), 154.0 (Cq), 163.4

(d, $^{1}J_{C\text{-}F}$ = 249.8 Hz, Cq), 163.6 (d, $^{1}J_{C\text{-}F}$ = 250.2 Hz, Cq) ; ^{19}F NMR (282 MHz, $CDCl_3$): δ = -111.9, -111.5; HRMS (ESI) calcd. for $C_{24}H_{20}F_2NO_4$ $[M+H]^+$: 424.13549; found: 424.13553.

***tert*-Butyl-2,5-bis(4-*tert*-butylphenyl)-7-oxopyrano-[3,4-*b*]pyrrole-1(7*H*)-carboxylate (3e):** Eluant: PE/Et_2O 95/5, yield = 72% ; $C_{32}H_{37}NO_4$; Rf (PE/Et_2O: 80/20) = 0.38; colorless oil; IR (ATR): ν = 2960, 2903, 2870, 1765, 1728, 1477, 1285, 1148, 824; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 9H), 1.35 (s, 9H), 1.55 (s, 9H), 6.37 (s, 1H), 6.93 (s, 1H), 7.40-7.47 (m, 6H), 7.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4 (CH_3), 31.29 (CH_3), 31.34 (CH_3), 34.8 (Cq), 86.2 (Cq), 96.9 (CH), 106.2 (CH), 117.5 (Cq), 125.0 (CH), 125.4 (CH), 125.8 (CH), 128.2 (Cq), 128.4 (CH), 129.7 (Cq), 134.6 (Cq), 144.8 (Cq), 148.5 (Cq), 152.4 (Cq), 152.9 (Cq), 154.1 (Cq), 154.8 (Cq); HRMS (ESI) calcd. for $C_{32}H_{38}NO_4$ $[M+H]^+$: 500.27954; found: 500.27966.

***tert*-Butyl-2,5-dibutyl-7-oxopyrano[3,4-*b*]pyrrole-1(7*H*)-carboxylate (3f):** Eluant: PE/Et_2O 95/5; yield = 66%; $C_{20}H_{29}NO_4$; Rf (PE/Et_2O: 80/20) = 0.39; yellow oil; IR (ATR): ν = 2957, 2931, 2872, 1729 (br), 1305, 1150, 840; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (m, 6H), 1.33-1.44 (m, 4H), 1.59-1.72 (m, 13H), 2.50 (t, J = 7.4 Hz, 2H), 2.84 (t, J = 7.4 Hz, 2H), 6.01 (s, 1H), 6.16 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.89 (CH_3), 13.95 (CH_3), 22.2 (CH_2), 22.5 (CH_2), 27.6 (CH_3), 27.7 (CH_2), 29.4 (CH_2), 31.0 (CH_2), 33.3 (CH_2), 85.6 (Cq), 98.3 (CH), 104.6 (CH), 116.1 (Cq), 135.9 (Cq), 147.5 (Cq), 148.9 (Cq), 154.6 (Cq), 159.6 (Cq) ; HRMS (ESI) calcd. for $C_{20}H_{30}NO_4$ $[M+H]^+$: 348.21693; found: 348.21698.

***tert*-Butyl-2,5-diisopentyl-7-oxopyrano[3,4-*b*]pyrrole-1(7*H*)-carboxylate (3g):** Eluant: PE/Et_2O 95/5, yield = 75%; $C_{22}H_{33}NO_4$; Rf (PE/Et_2O: 95/5) = 0.20; yellow oil; IR (ATR): ν = 2956, 2928, 2870, 1729 (br), 1304, 1150, 841; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (app. t, J = 6.3 Hz, 12H), 1.50-1.61 (m, 6H), 1.65 (s, 9H), 2.50 (t, J = 7.2 Hz, 2H), 2.84 (t, J = 7.5 Hz, 2H), 6.02 (s, 1H), 6.17 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.4 (CH_3), 22.5 (CH_3), 25.9 (CH_2), 27.5 (CH_3), 27.6 (CH), 27.9 (CH), 31.6 (CH_2), 36.3 (CH_2), 37.8 (CH_2), 85.6 (Cq), 98.2 (CH), 104.4 (CH), 116.1 (Cq), 135.8 (Cq), 147.7 (Cq), 148.8 (Cq), 154.5 (Cq), 159.8 (Cq); HRMS (ESI) calcd. for $C_{22}H_{34}NO_4$ $[M+H]^+$: 376.24824; found: 376.24749.

General procedure for the synthesis of pyrroles (4)

$PtCl_2$ (5 mol%, 0.025 mmol, 6.6 mg) was added to a solution of **2** (0.5 mmol) in toluene (5 mL). Reaction mixture was stirred at 75 °C overnight, and then filtrated on a pad of celite with EtOAc. The filtrate was evaporated under vacuum, and the residues were purified by flash chromatography on silica gel to give compounds **4**.

1-(*tert*-Butyl) 2-methyl 5-phenyl-3-(phenylethynyl)-1*H*-pyrrole-1,2-dicarboxylate (4'a): Eluant: PE/AcOEt 95/5→80/20, yield = 64%; white solid; m.p.: 97-99 °C; $C_{25}H_{23}NO_4$; Rf (PE/Et_2O: 90/10) = 0.32; IR (ATR): ν = 3028, 2956, 1761, 1705, 1450, 1152, 760; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 9H), 3.96 (s, 3H), 6.38 (s, 1H), 7.32-7.36 (m, 3H), 7.38-7.46 (m, 5H), 7.52-7.57 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.3 (CH_3), 52.0 (CH_3), 82.9.0 (Cq), 85.9 (Cq), 93.5 (Cq), 113.0 (Cq), 114.2 (CH), 123.5 (Cq), 125.7 (Cq), 128.3 (CH), 128.43 (CH), 128.45 (CH), 128.84 (CH), 129.1 (CH), 131.2 (Cq), 131.7 (Cq), 138.4 (Cq), 148.9 (Cq), 160.5 (Cq). HRMS (ESI) calcd. for $C_{25}H_{24}NO_4$ $[M+H]^+$: 402.16998; found: 402.16917.

2-Benzyl 1-*ter*t-butyl 5-phenyl-3-(phenylethynyl)-1*H*-pyrrole-1,2-dicarboxylate (4a): Eluant: PE/AcOEt 95/5→90/10, yield = 70%; yellow oil; $C_{31}H_{27}NO_4$; Rf (PE/Et_2O: 90/10) = 0.22; IR (ATR): ν = 3063, 3034, 2981, 2937, 1767, 1698, 1277, 1251, 1216, 1149, 1122, 1070, 752, 691; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 9H), 5.39 (s, 2H), 6.38 (s, 1H), 7.23-7.30 (m, 8H), 7.38-7.50 (m, 7H); ^{13}C NMR (75

MHz, $CDCl_3$): δ = 27.3 (CH_3), 67.0 (CH_2), 83.0 (Cq), 86.0 (Cq), 93.6 (Cq), 113.1 (Cq), 114.4 (CH), 123.4 (Cq), 125.3 (Cq), 128.2 (CH), 128.28 (CH), 128.32 (CH), 128.4 (CH), 128.6 (CH), 128.8 (CH), 129.1 (CH), 131.1 (Cq), 131.7 (Cq), 135.8 (Cq), 138.6 (Cq), 148.9 (Cq), 160.0 (Cq); HRMS (ESI) calcd. for $C_{31}H_{28}NO_4$ $[M+H]^+$: 478.20128; found: 478.20191.

2-Benzyl 1-*tert*-butyl 5-(4-methoxyphenyl)-3-((4-methoxyphenyl)-ethynyl)-1*H*-pyrrole-1,2-dicarboxylate (4b): Eluant : PE/AcOEt 80/20, yield = 68%; beige solid; m.p.: 74-76°C; $C_{33}H_{31}NO_6$; Rf (PE/AcOEt: 80/20) = 0.46; m.p.: 91-93°C; IR (ATR): ν = 2979, 2935, 2837, 2215, 1764, 1697, 1606, 1245; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 9H), 3.80 (s, 3H), 3.82 (s, 3H), 5.38 (s, 2H), 6.31 (s, 1H), 6.77 (m, 2H), 6.92 (m, 2H), 7.16 (m, 2H), 7.24-7.29 (m, 3H), 7.36 (m, 2H), 7.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.3 (CH_3), 55.38 (CH_3), 55.43 (CH_3), 66.8 (CH_2), 81.8 (Cq), 85.8 (Cq), 93.7 (Cq), 113.6 (Cq), 113.7 (CH), 113.9 (CH), 114.1 (CH), 115.6 (Cq), 123.4 (Cq), 124.7 (Cq), 128.1 (CH), 128.3 (CH), 128.6 (CH), 130.5 (CH), 133.2 (CH), 135.9 (Cq), 138.7 (Cq), 149.2 (Cq), 159.6 (Cq), 160.1 (Cq); HRMS (ESI) calcd. for $C_{33}H_{32}NO_6$ $[M+H]^+$: 538.22241; found: 538.22246.

2-Benzyl 1-*tert*-butyl 5-(4-(dimethylamino)phenyl)-3-((4-(dimethylamino)phenyl)ethynyl)-1*H*-pyrrole-1,2-dicarboxylate (4d): Eluant: PE/AcOEt 50/50, yield = 36%; $C_{35}H_{37}N_3O_4$; Rf (PE/AcOEt : 50/50) = 0.61; orange oil; IR (ATR): ν = 2978, 2888, 2802, 2208, 1762, 1695, 1606, 1149, 812; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 2.97 (s, 6H), 2.98 (s, 6H), 5.39 (s, 2H), 6.27 (s, 1H), 6.57 (m, 2H), 6.70 (m, 2H), 7.15 (m, 2H), 7.25-7.33 (m, 5H), 7.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4 (CH_3), 40.4 (CH_3), 40.5 (CH_3), 66.6 (CH_2), 81.4 (Cq), 85.4 (Cq), 95.0 (Cq), 110.5 (Cq), 111.7 (CH), 111.8 (CH), 113.6 (CH), 114.4 (Cq), 118.7 (Cq), 127.9 (CH), 128.2 (CH), 128.6 (CH), 130.0 (CH), 132.9 (CH), 136.2 (Cq), 139.8 (Cq), 149.6 (Cq), 150.1 (Cq), 150.7 (Cq), 160.3 (Cq); HRMS (ESI) calcd. for $C_{35}H_{38}N_3O_4$ $[M+H]^+$: 564.28568; found: 564.28601.

2-Benzyl 1-*tert*-butyl 5-butyl-3-(hex-1-ynyl)-1*H*-pyrrole-1,2-dicarboxylate (4f): Eluant: PE/Et_2O 95/5; yield = 48% ; $C_{27}H_{35}NO_4$; Rf (PE/Et_2O: 80/20) = 0.45; yellow oil; IR (ATR): ν = 2956, 2931, 2872, 2235, 1755, 1704, 1226, 1158; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85-0.94 (m, 6H), 1.33-1.62 (m, 17H), 2.28 (t, J = 6.9 Hz, 2H), 2.67 (t, J = 7.2 Hz, 2H), 5.32 (s, 2H), 5.97 (s, 1H), 7.31-7.48 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (CH_3), 13.9 (CH_3), 19.5 (CH_2), 22.1 (CH_2), 22.4 (CH_2), 27.1 (CH_2), 27.5 (CH_3), 30.79 (CH_2), 30.84 (CH_2), 66.5 (CH_2), 73.9 (Cq), 85.2 (Cq), 95.1 (Cq), 112.8 (CH), 114.6 (Cq), 125.0 (Cq), 128.0 (CH), 128.2 (CH), 128.5 (CH), 136.2 (Cq), 140.6 (Cq), 149.2 (Cq), 160.3 (Cq); HRMS (ESI) calcd. for $C_{27}H_{36}NO_4$ $[M+H]^+$: 438.26389; found: 438.26384.

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Graphical abstract

