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A Copper-Catalyzed *N*-Alkynylation Route to 2-Substituted *N*-Alkynyl Pyrroles and Their Cyclization into Pyrrolo[2,1-*c*]oxazin-1-ones: A Formal Total Synthesis of Peramine

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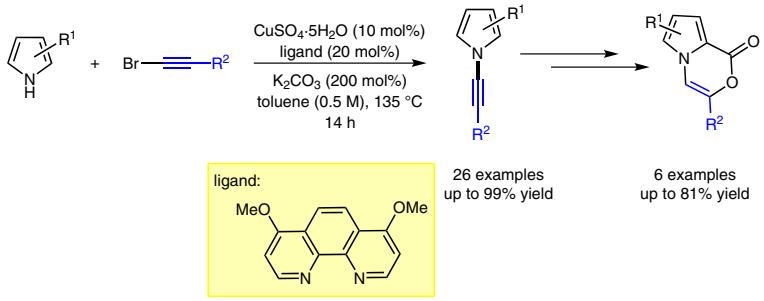

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Abstract Screening of a variety of ligands and reaction conditions for the copper-catalyzed cross-coupling of alkynyl bromides with pyrroles, reveals that the use of the phenanthroline ligand 4,7-dimethoxy-1,10-phenanthroline affords a range of ynpyrroles in good to moderate yields. Furthermore, the utility of these ynpyrroles is demonstrated in the preparation of a series of pyrrolo[2,1-*c*][1,4]oxazin-1-ones and a formal total synthesis of the pyrrole natural product peramine.

Key words cross-coupling, alkynes, nitrogen heterocycles, cyclization, peramine

Nitrogen-substituted alkynes have a relatively long history and yet have undergone a resurgence of interest recently. In 1892, Bode attempted the synthesis of an *N*-alkynylamine (ynamine).[1] However, more than half a century passed before the first successful synthesis of an ynamine was reported.[2] This was followed by reports of a wealth of transformations of these ynamines.[3] Despite this early interest, the lack of general routes for their preparation and the general instability of these ynamines diminished their usefulness in synthetic chemistry. This area has witnessed a renaissance with a focus on *N*-alkynylamides (ynamides), which are more stable than ynamines, yet participate in a wide range of synthetically useful transformations.[4] The synthetic utility of ynamides was further increased with reports of their preparation utilizing cross-coupling reactions inspired by Buchwald's work on copper-catalyzed *N*-arylations of amides,[5] or via mild oxidative cross-coupling strategies.[6] These cross-coupling reactions have been successfully applied to the preparation of *N*-alkynyl sulfonamides,[7–11] amides,[8–12] ureas,[8–10,12] carbamates,[8–12] imides,[13] imines,[14] and sulfoximines.[15] Application to the preparation of *N*-alkynyl heterocycles has been somewhat limited, and include examples of *N*-alkynyl indoles,[9–11] benzimidazoles,[16,17] carbazoles,[18] indazoles,[17] pyrazoles,[17] and imidazoles.[16,17] However, only one report of the preparation of *N*-alkynyl pyrroles via cross-coupling has appeared.[10]

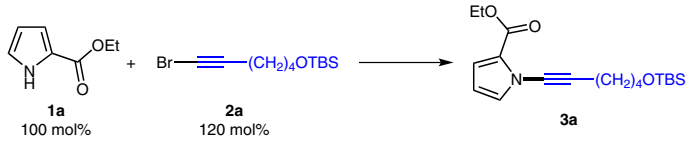
Our interest in *N*-alkynyl azoles as synthetic intermediates[19,20] has led us to explore the chemistry of *N*-alkynyl pyrroles (ynpyrroles). Due to the prevalence of pyrrole in both natural products and pharmaceuticals, we were interested to establish if ynpyrroles could serve as valuable intermediates in the synthesis of unique chemical scaffolds.[21] Most of the available syntheses of ynpyrroles involve elimination of *N*-halovinyl pyrroles using alkyllithium bases and thus are very limited in substrate scope.[22] We reasoned that a cross-coupling route to ynpyrroles would be much more versatile; however, through our investigations, it became clear that the available cross-coupling protocol for forming *N*-alkynyl pyrroles was also limited in scope. In particular, we found that when using this previously reported methodology, 2-substituted pyrroles did not participate in the cross-coupling with alkynyl bromides.[10] Thus, we set out to establish conditions that could efficiently cross-couple 2-substituted pyrroles with alkynyl bromides, and also demonstrate the synthetic utility of the subsequently formed ynpyrroles.

Our initial exploration focused on identifying conditions that could efficiently cross-couple 2-carboalkoxypyrrole **1a** and alkynyl bromide **2a** (Table 1). We began our search with a handful of established catalytic systems (Table 1, entries 1–5). Conditions previously reported by Hsung[10] for the synthesis of a handful of ynpyrroles (Table 1, entry 1) failed to generate **3a** in a detectable amount. We found that our previous conditions for synthesizing ynimidazoles[16] gave ynpyrrole **3a** in a 15% yield (Table 1, entry 4). Optimization of the conditions of entry 4 led to the formation of **3a** in a 46% yield, a modest gain by utilizing ligand **L1** (Table 1, entry 6). Changing from CuI as a precatalyst to

$CuSO_4·5H_2O$, together with a screen of a variety of phenanthroline-based ligands led to the formation of **3a** in an 88% yield, using 4,7-dimethoxy-1,10-phenanthroline (**L7**) and K_2CO_3 in toluene at 115 °C (Table 1, entry 7). **L7** proved to be a significantly better ligand than other phenanthrolines under identical conditions (Table 1, entries 8–11); further changes to the conditions of entry 7 only led to diminished yields (Table 1, entries 12–16). Considering the $CuSO_4$ precatalyst is a pentahydrate, we were not surprised to find that distillation of the toluene prior to degassing was not necessary for obtaining **3a** in a good yield (Table 1, entry 17).

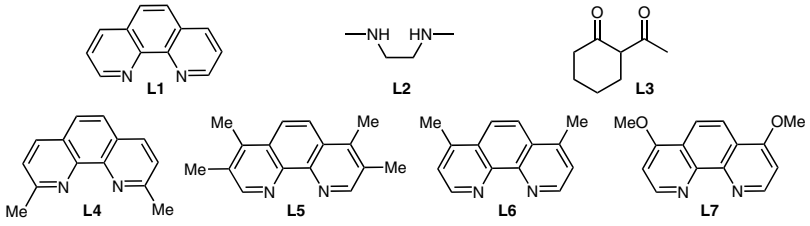
With improved conditions for the synthesis of **3a** established (Table 1, entry 7), the substrate scope was explored. A variety of alkynyl bromides participated in the cross-coupling; however, we noticed a significant effect of reaction temperature on the success of the coupling (Scheme 1, products **3a–d**). While the isolated yields of **3a** and **3b** were

Table 1 Optimization of Ynpyrrole **3a** Synthesis[a]



1a 100 mol% **2a** 120 mol% **3a**

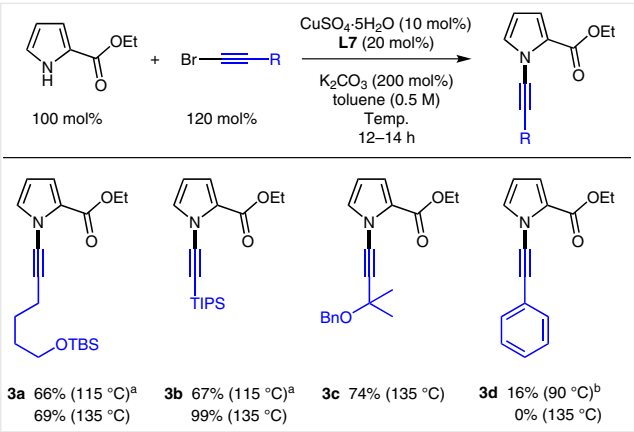
Entry	Precatalyst	Ligand	Base	Solvent	Temp (°C)	Yield (%)[b]
1	$CuSO_4·5H_2O$	**L1**	K_3PO_4	toluene	80	<5
2[c]	$FeCl_3$	**L2**	K_2CO_3	toluene	90	<5
3[d]	CuCN	**L2**	K_3PO_4	toluene	110	<5
4[e,f]	CuI	**L3**	Cs_2CO_3	dioxane	50	15
5[g]	CuO	n/a	KOH	dioxane	80	<5
6[f]	CuI	**L1**	Cs_2CO_3	dioxane	115	46
7	$CuSO_4·5H_2O$	**L7**	**K_2CO_3**	**toluene**	**115**	**88**
8	$CuSO_4·5H_2O$	**L1**	K_2CO_3	toluene	115	24
9	$CuSO_4·5H_2O$	**L4**	K_2CO_3	toluene	115	<5
10	$CuSO_4·5H_2O$	**L5**	K_2CO_3	toluene	115	<5
11	$CuSO_4·5H_2O$	**L6**	K_2CO_3	toluene	115	62
12	CuI	**L7**	K_2CO_3	toluene	115	21
13	$CuSO_4·5H_2O$	**L7**	K_2CO_3	dioxane	115	42
14	$CuSO_4·5H_2O$	**L7**	K_3PO_4	toluene	115	47
15	$CuSO_4·5H_2O$	**L7**	Cs_2CO_3	toluene	115	72
16	$CuSO_4·5H_2O$	**L7**	K_2CO_3	toluene	95	26
17	$CuSO_4·5H_2O$	**L7**	K_2CO_3	toluene[h]	115	75



L1 **L2** **L3** **L4** **L5** **L6** **L7**

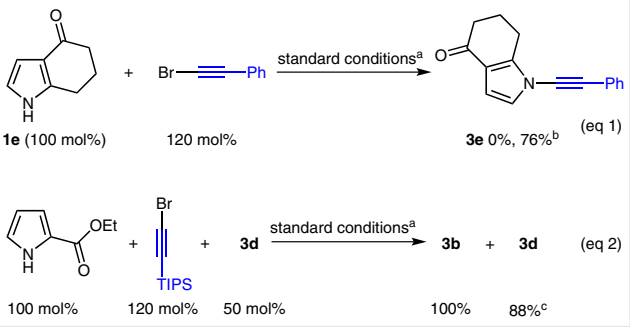
[a] Reactions were run with pyrrole **1a** (0.2 mmol), alkynyl bromide **2a** (0.24 mmol), Cu catalyst (0.02 mmol), ligand (0.04 mmol), base (0.4 mmol), solvent (0.4 mL), Temp (°C), 14 h.
[b] Yields were calculated by NMR using TCE (1,1,2,2-tetrachloroethane) as an internal standard.
[c] Using 1.0 mL of toluene (0.2 M).
[d] Using CuCN (0.01 mmol), **L2** (0.02 mmol), and 2.0 mL of toluene (0.1 M).
[e] Using CuI (0.01 mmol).
[f] 3 Å MS were added.
[g] Using CuO (0.004 mmol) and 0.66 mL of toluene (0.3 M).
[h] Toluene was used as received and degassed prior to use.

moderate at 115 °C, a small gain in yield was observed when increasing the temperature to 135 °C for **3a** and a rather substantial increase in yield was observed for substrate **3b**. Compound **3c**, which contains a benzyl propargyl ether, was formed in good yields at 135 °C, while compound **3d** was not formed at 135 °C and was only isolable in poor yields when the reaction temperature was lowered to 90 °C. (Bromoethynyl)benzene is a common cross-coupling partner in the synthesis of ynazoles and ynamides and we were curious why the yield of **3d** was so low.



Scheme 1 Scope of alkynyl bromides coupling to **1a**. *Reaction conditions*: pyrrole (0.2 mmol), alkynyl bromide (0.24 mmol), $CuSO_4·5H_2O$ (0.02 mmol), **L7** (0.04 mmol), K_2CO_3 (0.4 mmol), toluene (0.4 mL), 135 °C , 12–14 h. [a] Reaction run at 115 °C. [b] Reaction run at 90 °C.

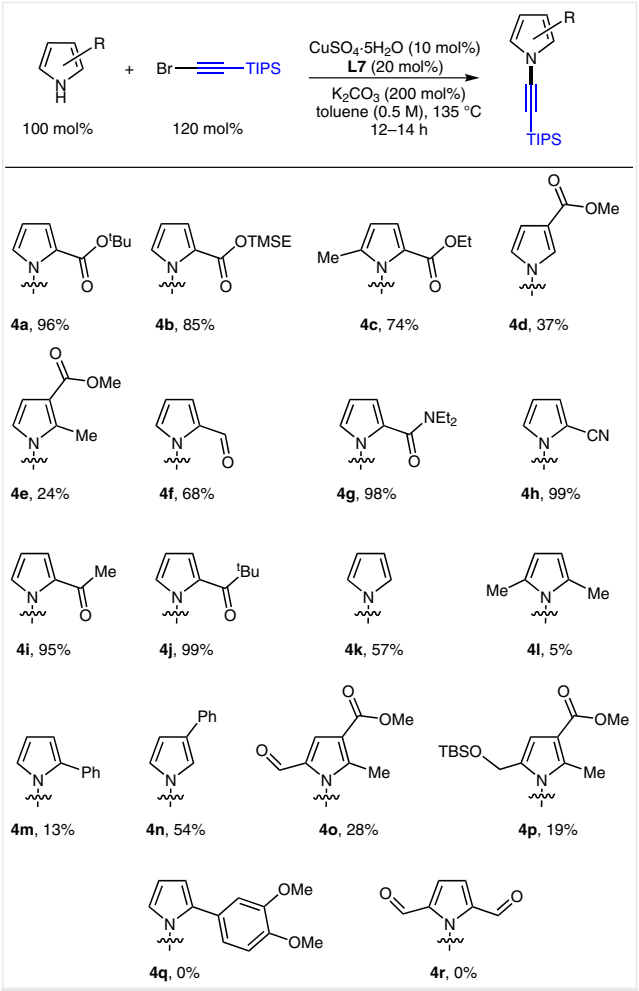
To further investigate the low yield of **3d**, we looked to a previously established pyrrole coupling partner for (bromoethynyl)benzene, pyrrole **1e**. Ynpyrrole **3e** (Scheme 2) has been reported by Hsung and co-workers via the coupling of (bromoethynyl)benzene and **1e**.[10] Using our newly established conditions from Table 1 at a reaction temperature of 135 °C, ynpyrrole **3e** (Scheme 2, eq 1) was not formed; however, running the cross-coupling at 80 °C, the desired ynpyrrole **3e** was isolated in a 76% yield. This suggests the poor yield of **3d** (Scheme 1), even at lower reaction temperatures, is an issue specific to pyrrole **1a** with (bromoethynyl)benzene rather than a general issue of (bromoethynyl)benzene as a coupling partner. Investigating the low yields of **3d** even further, we sought to determine if ynpyrrole **3d** could inhibit catalysis through an undesirable interaction with copper.[23] By running a cross-coupling in the presence of **3d** (Scheme 2, eq 2), we found ynpyrrole **3b** was formed quantitatively and **3d** was recovered in an excellent yield. These results suggest the low cross-coupling yields of **3d** were not from an undesirable interaction with copper or due to its decomposition under the reaction conditions, but due to an issue with generating the ynpyrrole. Considering the results, pyrrole **1a** and (bromoethynyl)benzene are poor cross-coupling partners, likely due to incompatible reactivities under our standard conditions, i.e., while the yields with pyrrole **1a** generally improve as reaction temperatures are increased, the yields with (bromoethynyl)benzene diminish with increasing temperatures.



Scheme 2 Cross-coupling with (bromoethynyl)benzene. [a] *Reaction conditions*: pyrrole (0.2 mmol), alkynyl bromide (0.24 mmol), $CuSO_4·5H_2O$ (0.02 mmol), **L7** (0.04 mmol), K_2CO_3 (0.4 mmol), toluene (0.4 mL), 135 °C, 12–14 h. [b] Reaction run at 80 °C. [c] Percent recovered.

We also sought to explore the reactivity and substrate scope of the pyrrole coupling partner (Scheme 3). The highly efficient cross-coupling to generate **3b** (Scheme 1) prompted us to use (bromoethynyl)triisopropylsilane at 135 °C as our standard conditions. In addition to pyrrole **1a**, a variety of esters were tolerated (Scheme 3, products **4a–e**,**o**,**p**), including esters at both the 2 and 3 positions of the pyrrole. A modest reduction in yield was observed in the synthesis of ynpyrrole **4c** compared to **3b**, likely the result of the increased sterics of a 2,5-disubstituted pyrrole. Various functional groups were tolerated in the 2-position (**4f–i**), including a bulky ketone (**4j**). Unsubstituted pyrrole gave a moderate yield (**4k**), while 2,5-dimethylpyrrole was a rather poor substrate (**4l**). In addition, phenyl-substituted pyrroles gave poor to moderate yields depending on the substitution and electronics (**4m**,**n**,**q**). Finally, trisubstituted ynpyrroles **4o** and **4p** could be formed in modest yields under our conditions.

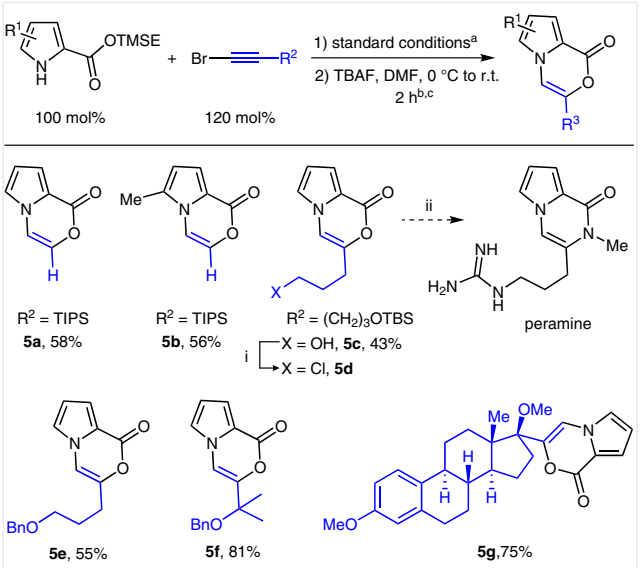
Considering the above results, the substitution on pyrrole appears to play an important role in this cross-coupling chemistry. Interestingly, both the most electron-deficient (**4o**,**r**) and the most electron-rich pyrroles gave poor yields (**4k**,**l**). This observed reactivity might be related to the variation in pK_a for these substrates. Pyrroles that are too acidic may form inactive copper aggregates[24] that diminish their reactivity, whereas substantially less acidic pyrroles may suffer from poor acid–base chemistry. It seems, for the conditions we have reported, that pyrroles with a single electron-withdrawing group at the 2-position display the best reactivity (**4a–c**,**f–j**). Thus, for pyrroles with significantly different electronics or sterics, a separate optimization of ligand and coupling conditions may be required.



Scheme 3 Scope of the pyrroles in cross-coupling

During our investigations, we were intrigued to find that deprotection of ynpyrrole **4b** with TBAF afforded compound **5a** as the sole product (Scheme 4). The pyrrole[2,1-*c*]oxazin-1-one **5a** is presumably formed by cyclization of the initially formed carboxylate (**5b′**,**c′**,**e′**–**g′**, see the experimental section). We decided to explore this result by examining this two-step cross-coupling/cyclization sequence for a variety of pyrrole and alkynyl bromide coupling partners (Scheme 4). Both 2-(trimethylsilyl)ethylcarboxylate- and 5-methyl-2-(trimethylsilyl)ethylcarboxylate-substituted ynpyrroles participate in this reaction (**5a**,**b**). In addition, a variety of alkynyl bromides were also tolerated, including those with large alkyne substituents. This procedure allowed for the synthesis of the novel estradiol analogue **5g** in a high yield in only four steps from ethinyl estradiol.

To further explore the utility of this two-step cross-coupling/cyclization procedure, we used this transformation to complete a formal total synthesis of the rye grass endophytic fungal alkaloid peramine.[25] Peramine is one of



Scheme 4 Synthesis of substituted pyrrolo[2,1-*c*]oxazin-1-ones. [a] *Reaction conditions*: pyrrole (0.2 mmol), alkynyl bromide (0.24 mmol), $CuSO_4·5H_2O$ (0.02 mmol), **L7** (0.04 mmol), K_2CO_3 (0.4 mmol), toluene (0.4 mL), 135 °C, 12–14 h. [b] 1.25 equiv of TBAF per silyl protecting group. [c] Yields calculated over two steps. (i) CH_2Cl_2, r.t., CCl_4 (9 equiv), PPh_3 (3 equiv), 70%; (ii) See ref. 27.

several herbivore-toxic alkaloids produced by epichloae fungi associated with cool-season grasses.[26] Using our two-step sequence, alcohol **5c** was obtained in a modest yield. Subsequent chlorination of **5c** gave pyrrolo[2,1-*c*][1,4]oxazin-1-one **5d**, an intermediate in the total synthesis of the natural product peramine.[27] This route to **5d** obviates difficulties encountered in the preparation of this compound from alkylation and cyclization of 2-(trichloroacetyl)pyrrole, which affords only 15% of the cyclized product on large scale.[27]

In conclusion, we have demonstrated a new set of conditions for the synthesis of 2-substituted ynpyrroles and applied them to an expanded scope of substrates. This work also illustrates the advantages of optimizing and tailoring the cross-coupling conditions for separate classes of pyrrole coupling partners. Finally, we also demonstrated the use of ynpyrroles toward the synthesis of pyrrolo[2,1-*c*][1,4]oxazin-1-ones, applying this strategy to the formal synthesis of peramine and to the unique elaboration of ethinyl estradiol analogues.

All pyrroles were commercially available or synthesized using standard chemistry. Pyrroles purchased commercially were purified by column chromatography prior to use. For the synthesis of known pyrroles: ethyl 5-methyl-1*H*-pyrrole-2-carboxylate,[28a] methyl 2-methyl-1*H*-pyrrole-3-carboxylate,[28b] *N*,*N*-diethyl-1*H*-pyrrole-2-carboxamide,[28c] 2,2-dimethyl-1-(1*H*-pyrrol-2-yl)propan-1-one,[28d] 2-phenyl-1*H*-pyrrole,[28e] 3-phenyl-1*H*-pyrrole,[28f] see referenced materials. All

reactions were run under argon unless otherwise stated. Column chromatography was carried out on SiliaFlash P60 silica gel (230-400 mesh). Reactions were monitored by TLC on Merck silica gel 60 W F245 aluminium-backed TLC plates. Optical rotations were measured using a Perkin-Elmer 241 MC polarimeter. Melting points were recorded on a Buchi B-540 melting point apparatus and are uncorrected. IR spectra were obtained using a PerkinElmer Spectrum 100 FT-IR spectrophotometer using a diamond anvil ATR accessory. NMR spectra were recorded in ppm at 400 MHz (^{1}H) and 100 MHz (^{13}C) using an Agilent MR spectrometer. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, quin = quintet, m = multiplet, br s = broad singlet. NMR yields were calculated using 1,1,2,2-tetrachloroethane as internal standard. HRMS was performed using an Agilent 6530 Q-TOF spectrometer.

Pyrrole Starting Materials

Methyl 5-Formyl-2-methyl-1*H*-pyrrole-3-carboxylate (1b)

Under argon at 0 °C, $POCl_3$ (2.83 mL, 30 mmol) was added to DMF (2.71 mL, 35 mmol) dropwise and the mixture allowed to warm to r.t. After 20 min, the mixture was cooled back to 0 °C and methyl 2-methyl-1*H*-pyrrole-3-carboxylate (2.28 g, 16.4 mmol) was added in portions and the mixture subsequently warmed to r.t. and stirred for 3 h. Following completion, the mixture was diluted with H_2O and quenched with NaOAc·3H_2O (12 g), then Na_2CO_3 (5 g) was added carefully in portions. The resulting solid was filtered and washed with H_2O. Purification by column chromatography (hexanes/EtOAc, 1:1) gave the title compound as a white solid (1.86 g, 56%), which could be further purified by recrystallization from toluene; mp 154–156 °C.

IR: 3254, 1713, 1651, 1567, 1475, 1416, 1243, 1138, 1094, 1012, 868, 776, 684 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.43 (br s, 1 H, H-1), 9.42 (s, 1 H, CHO), 7.35 (d, *J* = 2.8 Hz, 1 H, H-4), 3.84 (s, 3 H, CO_2CH_3), 2.63 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.2, 164.6, 144.0, 130.4, 124.2, 115.0, 51.1, 13.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_8H_9NO_3Na$: 190.0475; found: 190.0473.

Methyl 5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-2-methyl-1*H*-pyrrole-3-carboxylate (1c)

To a solution of methyl 5-formyl-2-methyl-1*H*-pyrrole-3-carboxylate (168 mg, 1.0 mmol) in MeOH (2.0 mL) was added $NaBH_4$ (76 mg, 2.0 mmol). Following reaction completion (TLC), the mixture was diluted with sat. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL), washed with brine (20 mL) and dried over Na_2SO_4. Removal of the solvent gave the alcohol, which was taken forward without further purification. To the residue was added CH_2Cl_2 (5.0 mL), Et_3N (600 µL, 4.0 mmol), and DMAP (12 mg, 0.1 mmol). After cooling to 0 °C, TBSCl (200 mg, 1.3 mmol) was added, and the solution was allowed to warm to r.t. After reaction completion (TLC), the mixture was diluted with sat. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 25 mL), the combined extracts were washed with brine (20 mL) and dried over Na_2SO_4. Removal of the solvent and purification by column chromatography (hexanes/EtOAc, 5:1) gave the title compound as a white solid (123.5 mg, 44%); mp 55–58 °C.

IR: 3302, 2951, 2856, 1675, 1596, 1530, 1450, 1339, 1224, 1134, 1060, 1001, 834, 776 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (br s, 1 H, H-1), 6.31 (d, *J* = 2.8 Hz, 1 H, H-4), 4.58 (s, 2 H, CH_2), 3.77 (s, 3 H, CO_2CH_3), 2.48 (s, 3 H, CH_3), 0.89 (s, 9 H, ^{t}Bu), 0.05 (s, 6 H, Si-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 135.3, 129.1, 111.1, 107.1, 58.3, 50.6, 25.8, 18.3, 13.1, –5.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{26}NO_3SiNa$: 284.1676; found: 284.1677.

2-(Trimethylsilyl)ethyl 1*H*-Pyrrole-2-carboxylate (1d)

Ethyl pyrrole-2-carboxylate (278 mg, 2.0 mmol) was added to 2-(trimethylsilyl)ethanol (2.0 mL), followed by KO^{t}Bu (24 mg, 0.2 mmol). The mixture was then heated to 110 °C and stirred for 5 h. After completion, the mixture was diluted with H_2O (100 mL) and extracted with EtOAc (3 × 35 mL), the combined extracts were washed with brine (30 mL) and dried over Na_2SO_4. Removal of the solvent and purification by column chromatography (hexanes/EtOAc, 20:1) gave the product as a white solid (270 mg, 64%); mp 67–68 °C.

IR: 3311, 2954, 1679, 1555, 1414, 1316, 1168, 1127, 1031, 963, 837, 744 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.30 (br s, 1 H, H-1), 6.96–6.94 (m, 1 H, H-3), 6.91–6.89 (m, 1 H, H-5), 6.26–6.24 (m, 1 H, H-4), 4.39–4.35 (m, 2 H, O-CH_2), 1.12–1.07 (m, 2 H, Si-CH_2), 0.07 (s, 9 H, Si-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.4, 123.1, 122.6, 114.9, 110.3, 62.5, 17.4, –1.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{17}NO_2SiNa$: 234.0921; found: 234.0912.

2-(Trimethylsilyl)ethyl 5-Methyl-1*H*-pyrrole-2-carboxylate (1f)

Following the procedure outlined above for 2-(trimethylsilyl)ethyl 1*H*-pyrrole-2-carboxylate, the title compound was synthesized as a white solid (135 mg, 50%); mp 83–84 °C.

IR: 3306, 2952, 1662, 1491, 1329, 1228, 1142, 990, 836, 771 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.45 (br s, 1 H, H-1), 6.79 (s, 1 H, H-3), 5.94 (t, *J* = 3.2 Hz, 1 H, H-4), 4.40–4.30 (m, 2 H, O-CH_2), 2.31 (s, 3 H, CH_3), 1.12–1.06 (m, 2 H, Si-CH_2), 0.07 (s, 9 H, Si-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.7, 134.0, 121.3, 115.9, 108.7, 62.2, 17.4, 13.0, –1.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{19}NO_2SiNa$: 248.1077; found: 248.1081.

Alkynyl Bromides 2; General Procedure

All the alkynyl bromides were synthesized from the respective alkyne using the following general procedure: To a solution of alkyne (1.0 equiv) in acetone (0.2 M) was added NBS (1.2 equiv) and $AgNO_3$ (0.1 equiv). The mixture was allowed to stir open to the air for 4 h. Following completion, the acetone was removed and the residue taken up in hexanes. The organics were washed with sat. NH_4Cl, H_2O (× 2), and brine, and dried over Na_2SO_4. Removal of the solvent gave the previously reported, pure alkynyl bromides: [(6-bromohex-5-yn-1-yl)oxy](*tert*-butyl)dimethylsilane,[29a] 2-bromo-1-triisopropylsilyl acetylene,[29b] {[(4-bromo-2-methylbut-3-yn-2-yl)oxy]methyl}benzene,[29c] and 1-bromo-2-phenylacetylene.[16]

{[(5-Bromopent-4-yn-1-yl)oxy]methyl}benzene (2b)

Pale yellow oil (1.36 g, 93%).

IR: 2931, 2860, 1718, 1602, 1452, 1364, 1272, 1203, 1175, 1104, 1070, 909, 736, 712, 697 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.29 (m, 5 H, Ar-H), 4.52 (s, 2 H, Ph-CH_2), 3.56 (t, *J* = 5.6 Hz, 2 H, O-CH_2), 2.35 (t, *J* = 7.2 Hz, 2 H, CC-CH_2), 1.82 (quin, *J* = 6.4 Hz, 2 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 128.3, 127.58, 127.55, 79.6, 72.9, 68.5, 37.9, 28.4, 16.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{13}BrONa$: 275.0042; found: 275.0040.

(8*R*,9*S*,13*S*,14*S*,17*S*)-17-(Bromoethynyl)-3,17-dimethoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene (2c)

Pale yellow solid (980 mg, 96%); mp 113–115 °C; $[\alpha]_D$ –23.4 (*c* 1.0, CH_2Cl_2).

IR: 2931, 2195, 1609, 1575, 1498, 1452, 1379, 1279, 1254, 1236, 1096, 1041, 975, 860, 813, 781, 736, 673 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 8.4 Hz, 1 H, H-1), 6.71 (dd, *J* = 8.8, 3.2 Hz, 1 H, H-2), 6.62 (d, *J* = 2.8 Hz, 1 H, H-4), 3.77 (s, 3 H, O3-CH_3), 3.40 (s, 3 H, O17-CH_3), 2.90–2.82 (m, 2 H, C6-H_2), 2.38–2.29 (m, 1 H, C9-H), 2.28–2.18 (m, 2 H), 2.03–1.66 (m, 6 H), 1.52–1.31 (m, 4 H), 0.86 (s, 3 H, C13-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3, 137.7, 132.3, 126.2, 113.6, 111.3, 86.8, 81.1, 55.0, 53.3, 49.5, 47.7, 46.3, 43.3, 39.0, 36.2, 34.1, 29.7, 27.1, 26.4, 22.6, 12.6.

HRMS (CI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{28}O_2Br$: 403.1273; found: 403.1203.

Ynpyrroles 3 and 4; General Procedure

An 8 mL vial was charged with K_2CO_3 (55 mg, 0.4 mmol) and flame-dried and allowed to cool under vacuum. Once cooled, the vial was rapidly charged with $CuSO_4{\cdot}5H_2O$ (5 mg, 0.02 mmol), 4,7-dimethoxy-1,10-phenanthroline (**L7**) (9.6 mg, 0.04 mmol), ethyl 1*H*-pyrrole-2-carboxylate **1** (27.8 mg, 0.2 mmol) and an oven-dried stir bar. To the vial was then added freshly distilled toluene (0.4 mL) and the mixture sparged with argon for 10 min. Finally, the alkynyl bromide **2** was added and the mixture sparged for an additional 10 min. Following degassing, the vial was rapidly sealed with a Teflon cap and placed in an oil bath at 135 °C. After reaction completion, the mixture was allowed to cool to r.t. and directly loaded onto a silica gel column and purified with hexanes/EtOAc.

Ethyl 1-{6-[(*tert*-Butyldimethylsilyl)oxy]hex-1-yn-1-yl}-1*H*-pyrrole-2-carboxylate (3a)

Pale yellow oil (48.3 mg, 69%).

IR: 2930, 2274, 1721, 1465, 1422, 1259, 1104, 835, 733 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (dd, *J* = 2.8, 2.0 Hz, 1 H, H-3), 6.90 (dd, *J* = 3.6, 1.6 Hz, 1 H, H-5), 6.15 (dd, *J* = 4.0, 2.8 Hz, 1 H, H-4), 4.30 (q, *J* = 7.2 Hz, 2 H, O-CH_2), 3.65 (t, *J* = 5.6 Hz, 2 H, SiO-CH_2), 2.46–2.41 (m, 2 H, CC-CH_2), 1.72–1.64 (m, 4 H, CH_2CH_2), 1.34 (t, *J* = 7.2 Hz, 3 H, OCH_2-CH_3), 0.88 (s, 9 H, Si-^{t}Bu), 0.04 (s, 6 H, Si-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6, 131.5, 125.5, 117.6, 109.8, 72.6, 69.2, 62.6, 60.2, 31.9, 25.9, 25.1, 18.3, 18.1, 14.3, –5.3.

HRMS (CI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{32}NO_3Si$: 350.2151; found: 350.2145.

Ethyl 1-[(Triisopropylsilyl)ethynyl]-1*H*-pyrrole-2-carboxylate (3b)

Pale yellow oil (64.0 mg, 99%).

IR: 2942, 2187, 1724, 1457, 1255, 1099, 1074, 996, 882, 731, 675 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.04 (dd, *J* = 2.8, 1.6 Hz, 1 H, H-3), 6.93 (dd, *J* = 3.6, 1.6 Hz, 1 H, H-5), 6.18 (dd, *J* = 3.6, 2.8 Hz, 1 H, H-4), 4.32 (q, *J* = 7.2 Hz, 2 H, O-CH_2), 1.34 (t, *J* = 7.2 Hz, 3 H, OCH_2-CH_3), 1.16–1.12 (m, 21 H, Si-^{i}Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 131.9, 126.1, 118.2, 110.3, 94.6, 68.3, 60.3, 18.6, 14.4, 11.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{29}NO_2SiNa$: 342.1860; found: 342.1854.

Ethyl 1-[3-(Benzyloxy)-3-methylbut-1-yn-1-yl]-1*H*-pyrrole-2-carboxylate (3c)

Clear oil (45.8 mg, 74%).

IR: 2984, 2269, 1716, 1422, 1262, 1207, 1154, 1100, 731, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.24 (m, 5 H, Ph), 7.01 (dd, *J* = 2.8, 1.6 Hz, 1 H, H-3), 6.96 (dd, *J* = 4.0, 1.6 Hz, 1 H, H-5), 6.21 (dd, *J* = 4.0, 2.8 Hz, 1 H, H-4), 4.75 (s, 2 H, Ph-CH_2), 4.33 (q, *J* = 7.2 Hz, 2 H, O-CH_2), 1.67 (s, 6 H, CH_3), 1.36 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 139.1, 131.3, 128.2, 127.7, 127.2, 126.0, 118.3, 110.3, 71.1, 70.8, 66.6, 60.3, 28.8, 14.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{21}NO_3Na$: 334.1414; found: 334.1431.

Ethyl 1-(Phenylethynyl)-1*H*-pyrrole-2-carboxylate (3d)

Pale yellow oil (7.9 mg, 16%).

IR: 2981, 2261, 1713, 1459, 1423, 1263, 1169, 1101, 754 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.52 (m, 2 H, *o*-Ar-H), 7.38–7.30 (m, 3 H, *m*-,*p*-Ar-H), 7.13 (dd, *J* = 3.2, 1.6 Hz, 1 H, H-5), 7.00 (dd, *J* = 3.6, 1.6 Hz, 1 H, H-3), 6.25 (dd, *J* = 3.6, 3.2 Hz, 1 H, H-4), 4.35 (q, *J* = 7.2 Hz, 2 H, O-CH_2), 1.36 (t, *J* = 7.2 Hz, 3 H, OCH_2-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5, 131.4, 131.0, 128.2, 128.1, 125.9, 122.1, 118.3, 110.5, 81.3, 69.4, 60.3, 14.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{13}NO_2Na$: 262.0838; found: 262.0840.

1-(Phenylethynyl)-1,5,6,7-tetrahydro-4*H*-indol-4-one (3e)

Pale yellow solid (35.7 mg, 76%); mp 101–103 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.46 (m, 2 H, *o*-Ar-H), 7.40–7.32 (m, 3 H, *p*-,*m*-Ar-H), 6.84 (d, *J* = 3.2 Hz, 1 H, H-2), 6.58 (d, *J* = 3.2 Hz, 1 H, H-3), 2.91 (t, *J* = 6.0 Hz, 2 H, H-5), 2.50 (t, *J* = 5.6 Hz, 2 H, H-7), 2.24–2.15 (m, 2 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.7, 147.1, 131.5, 128.7, 128.4, 124.7, 121.4, 121.3, 107.1, 79.4, 70.6, 37.6, 23.2, 21.8.

***tert*-Butyl 1-[(Triisopropylsilyl)ethynyl]-1*H*-pyrrole-2-carboxylate (4a)**

Clear oil (66.8 mg, 96%).

IR: 2942, 2185, 1718, 1546, 1457, 1268, 1172, 1099, 1073, 882, 730 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (dd, *J* = 2.4, 1.2 Hz, 1 H, H-3), 6.81 (dd, *J* = 4.0, 2.0 Hz, 1 H, H-5), 6.14 (dd, *J* = 4.0, 3.2 Hz, 1 H, H-4), 1.55 (s, 9 H, O-^{t}Bu), 1.13 (m, 21 H, Si-^{i}Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4, 131.3, 127.5, 117.3, 110.0, 94.9, 81.0, 68.1, 28.2, 18.6, 11.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{33}NO_2SiNa$: 370.2173; found: 370.2184.

2-(Trimethylsilyl)ethyl 1-[(Triisopropylsilyl)ethynyl]-1*H*-pyrrole-2-carboxylate (4b)

Clear oil (66.2 mg, 85%).

IR: 2944, 2187, 1721, 1458, 1420, 1252, 1096, 1073, 836, 731 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.04 (dd, *J* = 3.2, 2.0 Hz, 1 H, H-3), 6.91 (dd, *J* = 3.2, 1.2 Hz, 1 H, H-5), 6.17 (dd, *J* = 3.6, 2.4 Hz, 1 H, H-4), 4.39–4.33 (m, 2 H, O-CH_2), 1.16–1.12 (m, 21 H, Si-^{i}Pr), 1.12–1.06 (m, 2 H, Si-CH_2), 0.06 (s, 9 H, Si-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 131.8, 126.3, 118.0, 110.2, 94.6, 68.2, 62.5, 18.6, 17.5, 11.3, –1.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{37}NO_2Si_2Na$: 414.2255; found: 414.2273.

Ethyl 5-Methyl-1-[(triisopropylsilyl)ethynyl]-1*H*-pyrrole-2-carboxylate (4c)

Clear oil (49.6 mg, 74%).

IR: 2942, 2865, 2183, 1719, 1492, 1259, 1133, 1026, 882, 795, 752 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.86 (d, *J* = 3.6 Hz, 1 H, H-3), 5.95 (dd, *J* = 3.6, 0.8 Hz, 1 H, H-4), 4.31 (q, *J* = 7.2 Hz, 2 H, O-CH_2), 2.34 (s, 3 H, C5-CH_3), 1.32 (t, *J* = 7.2 Hz, 3 H, OCH_2-CH_3), 1.18–1.12 (m, 21 H, Si-^{i}Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 140.1, 125.1, 118.2, 108.6, 93.0, 72.3, 60.0, 18.6, 14.4, 12.9, 11.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{31}NO_2SiNa$: 356.2016; found: 356.2016.

Methyl 1-[(Triisopropylsilyl)ethynyl]-1*H*-pyrrole-3-carboxylate (4d)

Clear oil (22.8 mg, 37%).

IR: 2944, 2865, 2189, 1721, 1556, 1495, 1246, 1201, 1119, 1068, 982, 882, 755 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.49 (t, *J* = 2.0 Hz, 1 H, H-2), 6.82 (dd, *J* = 2.4, 1.6 Hz, 1 H, H-5), 6.57 (dd, *J* = 3.2, 1.6 Hz, 1 H, H-4), 3.81 (s, 3 H, O-CH_3), 1.14–1.06 (m, 21 H, Si-^{i}Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 129.6, 125.5, 117.6, 110.9, 95.1, 66.5, 51.3, 18.5, 11.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{28}NO_2Si$: 306.1884; found: 306.1888.

Methyl 2-Methyl-1-[(triisopropylsilyl)ethynyl]-1*H*-pyrrole-3-carboxylate (4e)

Clear oil (15.3 mg, 24%).

IR: 2943, 2865, 2187, 1713, 1577, 1438, 1304, 1243, 1080, 915, 882, 783, 711 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.73 (d, *J* = 2.8 Hz, 1 H, H-5), 6.49 (d, *J* = 2.8 Hz, 1 H, H-4), 3.80 (s, 3 H, O-CH_3), 2.59 (s, 3 H, C2-CH_3), 1.14–1.09 (m, 21 H, Si-^{i}Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 139.9, 122.7, 112.8, 110.7, 93.6, 70.3, 51.0, 18.5, 11.7, 11.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{30}NO_2Si$: 320.2040; found: 320.2043.

1-[(Triisopropylsilyl)ethynyl]-1*H*-pyrrole-2-carbaldehyde (4f)

Pale yellow oil (37.3 mg, 68%).

IR: 2944, 2866, 2189, 1682, 1543, 1462, 1417, 1385, 883, 763 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.87 (s, 1 H, CHO), 7.13 (dd, *J* = 2.8, 1.2 Hz, 1 H, H-5), 7.03–6.99 (m, 1 H, H-3), 6.34–6.29 (m, 1 H, H-4), 1.17–1.10 (m, 21 H, Si-^{i}Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.7, 134.5, 131.9, 118.6, 111.7, 92.6, 70.2, 18.5, 11.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{25}NOSiNa$: 298.1598; found: 298.1602.

***N*,*N*-Diethyl-1-[(triisopropylsilyl)ethynyl]-1*H*-pyrrole-2-carboxamide (4g)**

Pale yellow oil (67.8 mg, 98%).

IR: 2941, 2865, 2183, 1632, 1461, 1272, 1092, 1067, 995, 882, 791, 735 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.87 (dd, *J* = 3.2, 1.6 Hz, 1 H, H-5), 6.23 (dd, *J* = 3.6, 1.2 Hz, 1 H, H-3), 6.10 (dd, *J* = 3.6, 2.8 Hz, 1 H, H-4), 3.41 (br s, 4 H, N-CH_2), 1.16 (t, *J* = 7.2 Hz, 6 H, NCH_2-CH_3), 1.07 (s, 21 H, Si-^{i}Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.1, 130.7, 126.3, 110.2, 109.4, 94.3, 67.5, 18.5, 11.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{34}N_2OSiNa$: 369.2333; found: 369.2350.

1-[(Triisopropylsilyl)ethynyl]-1*H*-pyrrole-2-carbonitrile (4h)

Pale yellow oil (58.8 mg, 99%).

IR: 2943, 2865, 2227, 2185, 1455, 1146, 1071, 882, 782 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.05 (dd, *J* = 3.2, 1.2 Hz, 1 H, H-5), 6.81 (dd, *J* = 3.6, 1.2 Hz, 1 H, H-3), 6.22 (dd, *J* = 4.0, 2.8 Hz, 1 H, H-4), 1.18–1.11 (m, 21 H, Si-^{i}Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.3, 121.0, 111.8, 110.8, 108.8, 91.9, 70.9, 18.4, 11.1.

HRMS (CI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{25}N_2Si$: 273.1787; found: 273.1786.

1-{1-[(Triisopropylsilyl)ethynyl]-1*H*-pyrrol-2-yl}ethan-1-one (4i)

Light orange oil (54.8 mg, 95%).

IR: 2942, 2864, 2184, 1673, 1454, 1253, 1076, 940, 881, 783, 734, 659 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.08 (dd, *J* = 2.8, 1.6 Hz, 1 H, H-5), 6.89 (dd, *J* = 4.0, 2.0 Hz, 1 H, H-3), 6.20 (dd, *J* = 4.0, 2.8 Hz, 1 H, H-4), 2.45 (s, 3 H, CO-CH_3), 1.14 (s, 21 H, Si-^{i}Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 186.4, 133.9, 133.0, 118.8, 110.4, 95.0, 68.1, 26.8, 18.6, 11.3.

HRMS (CI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{28}NOSi$: 290.1940; found: 290.1941.

2,2-Dimethyl-1-{1-[(triisopropylsilyl)ethynyl]-1*H*-pyrrol-2-yl}propan-1-one (4j)

Pale yellow oil (66.1 mg, 99%).

IR: 2942, 2865, 2182, 1661, 1448, 1409, 1325, 1182, 928, 881, 784, 732 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.02 (dd, *J* = 2.8, 1.2 Hz, 1 H, H-5), 6.84 (dd, *J* = 4.0, 1.2 Hz, 1 H, H-3), 6.16 (dd, *J* = 4.0, 3.2 Hz, 1 H, H-4), 1.33 (s, 9 H, O-^{t}Bu), 1.17–1.11 (m, 21 H, Si-^{i}Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.4, 132.2, 131.5, 116.8, 109.6, 95.6, 67.3, 43.5, 28.1, 18.6, 11.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{34}NOSi$: 332.2404; found: 332.2413.

1-[(Triisopropylsilyl)ethynyl]-1*H*-pyrrole (4k)

Clear oil (28.0 mg, 57%).

IR: 2942, 2865, 2185, 1480, 1313, 958, 882, 762, 721, 674 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.88 (t, *J* = 2.0 Hz, 2 H, H-2/5), 6.17 (t, *J* = 2.0 Hz, 2 H, H-3/4), 1.12 (s, 21 H, Si-^{i}Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 124.7, 110.0, 96.7, 64.4, 18.5, 11.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{26}NSi$: 248.1829; found: 248.1831.

2,5-Dimethyl-1-[(triisopropylsilyl)ethynyl]-1*H*-pyrrole (4l)

Clear oil (2.6 mg, 5%).

IR: 2941, 2865, 2169, 1693, 1541, 1463, 1397, 1195, 882, 794, 764, 675 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.73 (s, 2 H, H-3/4), 2.27 (s, 6 H, CH_3), 1.11 (s, 21 H, Si-^{i}Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.2, 106.5, 94.1, 70.6, 18.6, 12.5, 11.3.

HRMS (CI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{29}NSi$: 275.2069; found: 275.2068.

2-Phenyl-1-[(triisopropylsilyl)ethynyl]-1*H*-pyrrole (4m)

Clear oil (8.1 mg, 13%).

IR: 2923, 2864, 2177, 1727, 1469, 1323, 1247, 1180, 1072, 978, 882, 782, 753 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.69 (m, 2 H, *o*-Ar-H), 7.40–7.33 (m, 2 H, *m*-Ar-H), 7.33–7.27 (m, 1 H, *p*-Ar-H), 6.97 (dd, *J* = 3.2, 1.6 Hz, 1 H, H-5), 6.30 (dd, *J* = 3.6, 1.6 Hz, 1 H, H-3), 6.22 (dd, *J* = 3.6, 2.8 Hz, 1 H, H-4), 1.09–1.03 (m, 21 H, Si-^{i}Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.6, 131.3, 128.1, 127.6, 127.2, 126.7, 110.3, 108.9, 96.0, 68.1, 18.5, 11.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{30}NSi$: 324.2142; found: 324.2133.

3-Phenyl-1-[(triisopropylsilyl)ethynyl]-1*H*-pyrrole (4n)

Clear oil (34.9 mg, 54%).

IR: 2943, 2865, 2183, 1727, 1462, 1367, 1265, 1157, 1069, 988, 881, 736 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.49 (m, 2 H, *o*-Ar-H), 7.39–7.33 (m, 2 H, *m*-Ar-H), 7.23 (tt, *J* = 7.2, 1.2 Hz, 1 H, *p*-Ar-H), 7.17 (t, *J* = 2.0 Hz, 1 H, H-5), 6.93 (dd, *J* = 2.8, 2.0 Hz, 1 H, H-2), 6.49 (dd, *J* = 2.8, 1.6 Hz, 1 H, H-3), 1.15 (s, 21 H, Si-^{i}Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.1, 128.6, 126.3, 126.3, 125.8, 125.4, 120.7, 108.6, 96.6, 65.1, 18.6, 11.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{30}NSi$: 324.2142; found: 324.2130.

Methyl 5-Formyl-2-methyl-1-[(triisopropylsilyl)ethynyl]-1*H*-pyrrole-3-carboxylate (4o)

Clear oil (19.8 mg, 28%).

IR: 2944, 2865, 2186, 1718, 1682, 1568, 1502, 1440, 1234, 1134, 1072, 881, 773, 676 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.77 (s, 1 H, CHO), 7.31 (s, 1 H, H-4), 3.84 (s, 3 H, O-CH_3), 2.68 (s, 3 H, C2-CH_3), 1.18–1.11 (m, 21 H, Si-^{i}Pr).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.2, 163.8, 146.5, 132.7, 120.5, 114.8, 90.0, 76.2, 51.5, 18.5, 12.1, 11.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{29}NO_3SiNa$: 370.1809; found: 370.1815.

Methyl 5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-2-methyl-1-[(triisopropylsilyl)ethynyl]-1*H*-pyrrole-3-carboxylate (4p)

Clear oil (17.9 mg, 19%).

IR: 2944, 2864, 2185, 1714, 1593, 1544, 1462, 1224, 1070, 882, 835, 774, 676 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.40 (s, 1 H, H-4), 4.66 (s, 2 H, O-CH_2), 3.79 (s, 3 H, O-CH_3), 2.59 (s, 3 H, C2-CH_3), 1.15–1.09 (m, 21 H, Si-^{i}Pr), 0.88 (s, 9 H, Si-^{t}Bu), 0.04 (s, 6 H, Si-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 140.0, 134.1, 112.3, 109.2, 91.7, 73.6, 57.2, 51.0, 25.8, 18.6, 18.3, 12.0, 11.2, –5.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{45}NO_3Si_2Na$: 486.2830; found: 486.2827.

Pyrrolo[2,1-*c*][1,4]oxazin-1-ones 5; General Procedure

The ynpyrroles were synthesized following the previously outlined procedure. Following the synthesis and isolation of the appropriate ynpyrrole, the compounds were taken up in DMF (~0.5 M) and cooled to 0 °C. Once cooled, a 1 M solution of TBAF in THF was added dropwise (1.25 equiv TBAF per silyl protecting group) and the solution allowed to warm to r.t. After 2 h, the solution was diluted with sat. NH_4Cl (~10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were washed with brine and dried over Na_2SO_4. The solvent was then removed and the residue purified by column chromatography (yields are reported over 2 steps).

1*H*-Pyrrolo[2,1-*c*][1,4]oxazin-1-one (5a)

The product was prepared from pyrrole **4b**.

White solid (15.7 mg, 58%); mp 102–103 °C.

IR: 3125, 3112, 1746, 1718, 1532, 1474, 1379, 1300, 1205, 1076, 1024, 1001, 886, 730 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 4.8 Hz, 1 H, H-3), 7.11 (dd, *J* = 2.4, 1.6 Hz, 1 H, H-6), 7.03 (d, *J* = 4.8 Hz, 1 H, H-4), 6.81 (d, *J* = 4.4 Hz, 1 H, H-8), 6.55 (dd, *J* = 4.4, 2.4 Hz, 1 H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.9, 131.7, 121.1, 117.7, 115.9, 113.1, 109.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_7H_5NO_2Na$: 158.0212; found: 158.0213.

2-(Trimethylsilyl)ethyl-5-methyl-1-[(triisopropylsilyl)ethynyl]-1*H*-pyrrole-2-carboxylate (5b′)

IR: 2944, 2865, 2184, 1718, 1493, 1259, 1134, 837, 752, 676 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (d, *J* = 4.0 Hz, 1 H, H-3), 5.94 (dd, *J* = 4.0, 0.8 Hz, 1 H, H-4), 4.39–4.31 (m, 2 H, O-CH_2), 2.34 (d, *J* = 0.8 Hz, 3 H, C5-CH_3), 1.17–1.14 (m, 21 H, Si-^{i}Pr), 1.11–1.06 (m, 2 H, Si-CH_2), 0.06 (s, 9 H, Si-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 140.0, 125.3, 118.1, 108.6, 93.0, 72.3, 62.2, 18.6, 17.5, 12.9, 11.3, –1.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{39}NO_2Si_2Na$: 428.2412; found: 428.2429.

6-Methyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (5b)

White solid (16.8 mg, 56%); mp 106–107 °C.

IR: 3129, 3105, 2925, 1739, 1705, 1488, 1430, 1365, 1320, 1230, 1077, 1043, 977, 726 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 4.4 Hz, 1 H, H-3), 6.92 (dd, *J* = 4.4, 0.8 Hz, 1 H, H-8), 6.82 (d, *J* = 4.4 Hz, 1 H, H-4), 6.31 (dd, *J* = 4.0, 0.8 Hz, 1 H, H-7), 2.38 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 131.5, 130.2, 116.8, 115.7, 112.5, 106.1, 11.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_8NO_2$: 150.0550; found: 150.0547.

2-(Trimethylsilyl)ethyl-1-{5-[(*tert*-butyldimethylsilyl)oxy]pent-1-yn-1-yl}-1*H*-pyrrole-2-carboxylate (5c′)

Characterized with impurity.

IR: 2953, 2856, 1719, 1542, 1465, 1421, 1256, 1100, 938, 857, 833, 755, 731 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.99 (dd, *J* = 2.8, 1.6 Hz, 1 H, H-5), 6.87 (dd, *J* = 4.0, 1.6 Hz, 1 H, H-3), 6.14 (dd, *J* = 4.0, 2.8 Hz, 1 H, H-4), 4.37–4.31 (m, 2 H, CO_2-CH_2), 3.75 (t, *J* = 6.0 Hz, 2 H, SiO-CH_2), 2.49 (t, *J* = 6.8 Hz, 2 H, CC-CH_2-CH_2), 1.85–1.77 (m, 2 H, CH_2), 1.11–1.05 (m, 2 H, Si-CH_2), 0.89 (s, 9 H, Si-^{t}Bu), 0.06 (s, 15 H, Si-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 131.4, 125.6, 117.4, 109.8, 79.9, 72.5, 68.9, 62.4, 61.6, 61.3, 37.6, 31.6, 31.2, 25.9, 25.8, 18.3, 18.2, 17.3, 16.0, 14.8, –1.3, –1.4, –5.3, –5.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{37}NO_3Si_2Na$: 430.2204; found: 430.2223.

3-(3-Hydroxypropyl)-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (5c)

Clear oil (16.8 mg, 43%).

IR: 3407, 3116, 2928, 2874, 1717, 1683, 1532, 1478, 1388, 1363, 1215, 1035, 970, 892, 734 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.17 (m, 1 H, H-6), 7.04 (dd, *J* = 2.8, 1.6 Hz, 1 H, H-8), 6.85 (d, *J* = 0.8 Hz, 1 H, H-4), 6.50 (dd, *J* = 4.0, 2.4 Hz, 1 H, H-7), 3.71 (t, *J* = 6.4 Hz, 2 H, O-CH_2), 2.54 (t, *J* = 7.6 Hz, 2 H, CH_2), 1.96–1.87 (m, 2 H, CH_2), 1.84 (br s, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5, 143.8, 120.8, 116.5, 115.2, 112.9, 105.0, 61.2, 29.4, 27.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{11}NO_3Na$: 216.0631; found: 216.0627.

3-(3-Chloropropyl)-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (5d)

To a mixture of **5c** (10.0 mg, 0.05 mmol) and CCl_4 (44 µL, 0.45 mmol) in CH_2Cl_2 (0.1 mL) was added PPh_3 (25 mg, 0.15 mmol) in CH_2Cl_2 (0.1 mL) dropwise at r.t. The mixture was allowed to stir for 6 h, after which the solvent was removed and the residue purified by column chromatography (hexanes/EtOAc).

Clear oil (7.7 mg, 70%).

IR: 3118, 2959, 2922, 2850, 1747, 1723, 1688, 1532, 1478, 1364, 1290, 1215, 1078, 1035, 972, 734 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.21 (m, 1 H, H-6), 7.06 (dd, *J* = 2.8, 1.6 Hz, 1 H, H-8), 6.89–6.87 (m, 1 H, H-4), 6.53 (dd, *J* = 4.4, 2.8 Hz, 1 H, H-7), 3.60 (t, *J* = 6.0 Hz, 2 H, Cl-CH_2), 2.62 (t, *J* = 7.6 Hz, 2 H, CH_2), 2.20–2.10 (m, 2 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.2, 142.5, 120.8, 116.6, 115.5, 113.0, 105.5, 43.6, 29.0, 27.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{10}ClNO_2Na$: 234.0292; found: 234.0292.

2-(Trimethylsilyl)ethyl-1-[5-(benzyloxy)pent-1-yn-1-yl]-1*H*-pyrrole-2-carboxylate (5e′)

IR: 2952, 2852, 2272, 1715, 1542, 1464, 1421, 1257, 1100, 1028, 934, 857, 836, 733, 696 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.24 (m, 5 H, Ar-H), 6.96 (dd, *J* = 4.0, 2.0 Hz, 1 H, H-3), 6.89 (dd, *J* = 4.0, 2.0 Hz, 1 H, H-5), 6.15 (dd, *J* = 4.0, 3.2 Hz, 1 H, H-4), 4.54 (s, 2 H, Ph-CH_2), 4.40–4.30 (m, 2 H, CO_2-CH_2), 3.65 (t, *J* = 6.0 Hz, 2 H, O-CH_2), 2.55 (t, *J* = 7.2 Hz, 2 H, CC-CH_2), 1.98–1.88 (m, 2 H, CH_2), 1.12–1.06 (m, 2 H, Si-CH_2), 0.07 (s, 9 H, Si-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 138.4, 131.4, 128.2, 127.5, 127.4, 125.6, 117.4, 109.7, 72.8, 72.7, 68.7, 68.6, 62.4, 28.7, 17.3, 15.2, –1.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{29}NO_3SiNa$: 406.1809; found: 406.1826.

3-[3-(Benzyloxy)propyl]-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (5e)

Clear oil (31.1 mg, 55%).

IR: 3116, 3030, 2926, 2856, 1723, 1689, 1532, 1478, 1454, 1361, 1215, 1074, 1033, 970, 892, 732, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H, Ar-H), 7.21–7.17 (m, 1 H, H-6), 6.99 (dd, *J* = 2.4, 1.6 Hz, 1 H, H-8), 6.69 (d, *J* = 0.8 Hz, 1 H, H-4), 6.50 (dd, *J* = 4.0, 2.4 Hz, 1 H, H-7), 4.50 (s, 2 H, Ph-CH_2), 3.52 (t, *J* = 6.0 Hz, 2 H, O-CH_2), 2.52 (t, *J* = 7.2 Hz, 2 H, CH_2), 2.01–1.91 (m, 2 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.4, 143.7, 138.2, 128.3, 127.7, 127.6, 120.6, 116.5, 115.1, 112.7, 104.9, 72.8, 68.3, 27.5, 26.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{17}NO_3Na$: 306.1101; found: 306.1108.

2-(Trimethylsilyl)ethyl-1-[3-(benzyloxy)-3-methylbut-1-yn-1-yl]-1*H*-pyrrole-2-carboxylate (5f′)

IR: 2953, 2920, 2851, 2268, 1716, 1544, 1470, 1421, 1260, 1207, 1155, 1098, 1057, 944, 857, 836, 732. 695 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.23 (m, 5 H, Ar-H), 7.00 (dd, *J* = 2.4, 1.2 Hz, 1 H, H-3), 6.93 (dd, *J* = 4.0, 1.6 Hz, 1 H, H-5), 6.20 (dd, *J* = 4.0, 2.8 Hz, 1 H, H-4), 4.74 (s, 2 H, Ph-CH_2), 4.40–4.34 (m, 2 H, CO_2-CH_2), 1.66 (s, 6 H, CH_3), 1.14–1.06 (m, 2 H, Si-CH_2), 0.07 (s, 9 H, Si-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5, 139.1, 131.2, 128.2, 127.7, 127.2, 126.1, 118.1, 110.3, 71.1, 70.9, 66.6, 62.6, 28.9, 17.4, –1.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{29}NO_3SiNa$: 406.1809; found: 406.1826.

3-[2-(Benzyloxy)propan-2-yl]-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (5f)

White solid (45.8 mg, 81%); mp 89–90 °C.

IR: 3122, 2983, 2926, 1725, 1535, 1478, 1390, 1352, 1260, 1194, 1157, 1035, 958, 732, 696 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.32 (m, 4 H, *o*-,*m*-Ar-H), 7.30–7.24 (m, 1 H, *p*-Ar-H), 7.24–7.20 (m, 1 H, H-6), 7.13 (d, *J* = 0.8 Hz, 1 H, H-4), 7.09 (dd, *J* = 2.8, 1.6 Hz, 1 H, H-8), 6.54 (dd, *J* = 4.0, 2.8 Hz, 1 H, H-7), 4.50 (s, 2 H, Ph-CH_2), 1.61 (s, 6 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.9, 146.6, 138.4, 128.3, 127.4, 127.2, 121.3, 116.5, 115.3, 113.2, 104.9, 74.8, 65.1, 24.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}NO_3$: 284.1281; found: 284.1280.

2-(Trimethylsilyl)ethyl 1-{[(8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dimethoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl]ethynyl}-1*H*-pyrrole-2-carboxylate (5g′)

$[\alpha]_D$ –36.1 (*c* 1.0, CH_2Cl_2); mp 106–108 °C.

IR: 2940, 2263, 1715, 1609, 1499, 1463, 1421, 1251, 1097, 1040, 908, 858, 836, 731 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 4.8 Hz, 1 H, H-1), 7.07 (dd, *J* = 2.8, 1.6 Hz, 1 H, pyrrole H-5), 6.93 (dd, *J* = 4.0, 2.0 Hz, 1 H, pyrrole H-3), 6.71 (dd, *J* = 4.8, 2.8 Hz, 1 H, H-2), 6.63 (d, *J* = 2.8 Hz, 1 H, H-4), 6.21 (dd, *J* = 4.0, 2.8 Hz, 1 H, pyrrole H-4), 4.40–4.33 (m, 2 H, O-CH_2), 3.78 (s, 3 H, O3-CH_3), 3.50 (s, 3 H, O17-CH_3), 2.94–2.78 (m, 2 H, C6-H_2), 2.46–2.24 (m, 3 H, C9-H, C15-H, C16-H), 2.24–2.18 (m, 2 H, C11-H, C7-H), 1.96–1.80 (m, 4 H), 1.58–1.34 (m, 4 H), 1.13–1.05 (m, 2 H, Si-CH_2), 0.93 (s, 3 H, C13-CH_3), 0.06 (s, 9 H, Si-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 157.3, 137.9, 132.7, 131.3, 126.3, 126.2, 117.9, 113.7, 111.4, 110.2, 86.1, 79.9, 69.8, 62.5, 55.1, 53.4, 49.4, 48.0, 43.3, 39.2, 36.5, 34.2, 29.8, 27.2, 26.6, 22.8, 17.5, 12.8. –1.4.

HRMS (CI): *m*/*z* [M + H]$^+$ calcd for $C_{32}H_{44}NO_4Si$: 534.3040; found: 534.3023.

3-[(8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dimethoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl]-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (5g)

White solid (65.4 mg, 75%); mp 186–192 °C; $[\alpha]_D$ 37.1 (*c* 0.35, CH_2Cl_2).

IR: 2930, 1727, 1609, 1534, 1499, 1475, 1386, 1354, 1255, 1035, 869, 737 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (m, 1 H, pyrrolooxazine H-6), 7.15 (dd, *J* = 2.4, 1.2 Hz, 1 H, pyrrolooxazine H-8), 7.12 (d, *J* = 8.8 Hz, 1 H, H-1), 7.04 (s, 1 H, pyrrolooxazine H-4), 6.67 (dd, *J* = 8.4, 2.4 Hz, 1 H, H-2), 6.63–6.56 (m, 2 H, H-4, pyrrolooxazine H-7), 3.76 (s, 3 H), 3.24 (s, 3 H), 2.92–2.78 (m, 2 H, C6-H_2), 2.30–2.18 (m, 2 H), 2.16–2.02 (m, 2 H), 2.00–1.86 (m, 2 H), 1.85–1.76 (m, 1 H), 1.62–1.16 (m, 6 H), 0.99 (s, 3 H, C13-CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.4, 154.8, 144.4, 137.8, 132.5, 126.1, 121.0, 116.6, 115.1, 113.7, 113.3, 111.3, 108.2, 89.6, 55.1, 52.8, 48.7, 48.4, 43.3, 39.2, 33.9, 29.8, 29.7, 27.4, 26.3, 23.4, 14.6.

HRMS (CI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{32}NO_4$: 434.2331; found: 434.2312.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588736.

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