JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b00393 • Publication Date (Web): 21 Apr 2016

Just Accepted

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

3,4-Dihydro-2*H*-pyrrole-2-carbonitriles – Useful Intermediates in the Synthesis of Fused Pyrroles and 2,2'-Bipyrroles

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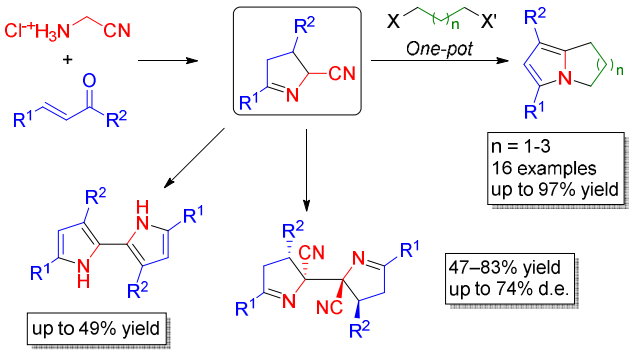


Abstract

Various heterocyclic structures containing the pyrrole moiety have been synthesized from easily accessible 3,4-dihydro-2*H*-pyrrole-2-carbonitriles in one pot procedures. 5,6,7,8-Tetrahydroindolizines, 2,3-dihydro-1*H*-pyrrolizines as well as 6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepines were obtained from these precursors in high yields in an alkylation/annulation sequence. The same conditions were applied in the synthesis of a 5,8-dihydroindolizine, which could easily be transformed to the corresponding indolizine

by dehydrogenation. Furthermore, oxidative couplings of 3,4-dihydro-2*H*-pyrrole-2-carbonitriles with copper(II)-salts furnished 2,2'-bipyrroles as well as 5,5'-bis(5-cyano-1-pyrrolines), depending on the reaction conditions. Overall, these methods give high yielding access to a variety of pyrrole-containing heterocyles in two steps from commercially available starting materials.

Introduction

The pyrrole ring is a ubiquitous heteroaromatic system found in countless natural products[1-4] as well as in synthetic drugs,[5-7] which can exert antimicrobial,[8-12] antiviral[13-17] as well as antitumor activity.[18-22] Pyrrole substructures are also contained in more complex heterocyclic systems found in nature such as the lamellarins,[23,24] the polygonatines,[25] (−)-rhazinilam,[26] (−)-chlorizidine A (Figure 1).[27] Likewise, there are also interesting synthetic "embedded" pyrroles such as the nonsteroidal anti-inflammatory drug ketorolac[28] or analogues of the cytotoxic antibiotic mitomycin.[29] Frequently occurring structural frameworks are the 5,6,7,8-tetrahydroindolizine or the 2,3-dihydro-1*H*-pyrrolizine ring system. The development of new synthetic methods for the preparation of these compounds has seen considerable progress in recent years[30-36] and 5,6,7,8-tetrahydroindolizines are now often being utilized as a key intermediate in the total synthesis of fully saturated indolizidine alkaloids.[37-40] Commonly applied strategies for the synthesis of 5,6,7,8-tetrahydroindolizines or 2,3-dihydro-1*H*-pyrrolizines are condensation reactions,[34,41,42] Lewis acid[36,43,44] or transition metal catalyzed cyclizations,[30,31,45-47] hydroacylations or hydroaminations,[33,48,49] cycloadditions[50,51] as well as the reduction of indolizines.[32,35] However, most of these methods are limited to the preparation of only one class of the mentioned compounds.

Herein, we report modular one pot procedures for the synthesis of 5,6,7,8-tetrahydroindolizines, 2,3-dihydro-1*H*-pyrrolizines and 6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepines as well as of 2,2'-bipyrroles and 5,5'-bis(5-cyano-1-pyrrolines) from readily available 3,4-dihydro-2*H*-pyrrole-2-carbonitriles as the common precursors. The starting materials can conveniently be prepared in one step from commercially available substrates in up to 90% yield.[52,53] To the best of our knowledge, no access to these compound classes of similar brevity and diversity from commercially available substrates has been reported so far.

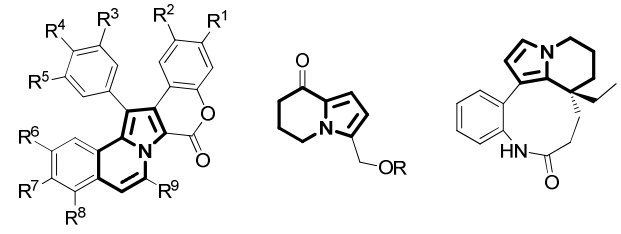
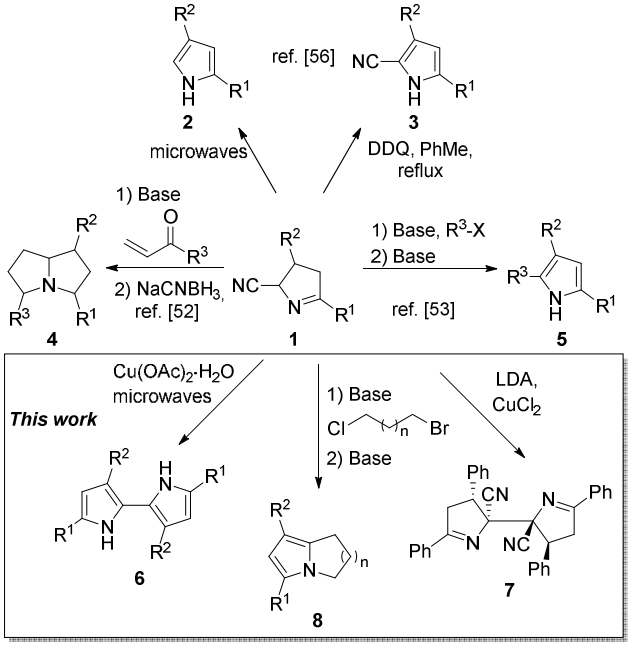


Figure 1. Biologically relevant compounds containing indolizines or pyrrolizines

Results and Discussion

3,4-Dihydro-2*H*-pyrrole-2-carbonitriles **1** can be obtained in a single step from commercially available aminoacetonitrile hydrochloride by condensation with enones via a 6π-electrocyclization.[52] This reaction was successfully employed in the synthesis of pyrrole-2-carboxylates and lamellarin alkaloids.[54,55] Cyanopyrrolines of this type can also be transformed to the corresponding pyrroles **2** or pyrrole-2-carbonitriles **3** by dehydrocyanation or dehydrogenation as well as to the corresponding pyrrolizidines **4** by

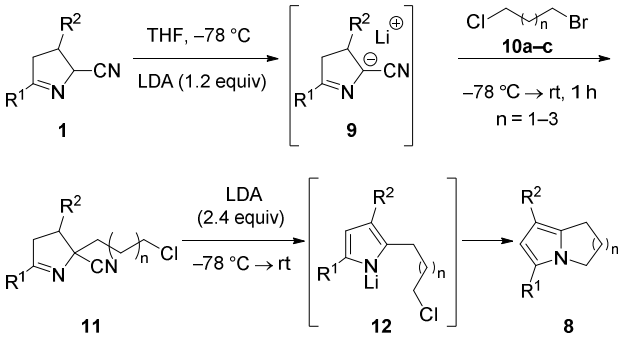
base catalyzed Michael-Addition with subsequent reductive amination.[52,56] Their α-alkylation produces 5-alkylated cyanopyrrolines which can be transformed to the corresponding 1*H*-pyrroles **5** in situ by further addition of base.[53] Here, we report oxidative dimerizations of compounds **1** as a simple entry to 2,2'-bipyrroles **6,** or 5,5'-bis(5-cyano-1-pyrrolines) **7** as well as a consecutive intramolecular annulation reaction with α,ω-dihalide electrophiles to furnish pyrrole-fused bicyclic structures **8** with variable ring size and a bridgehead nitrogen atom (Scheme 1).



Scheme 1. Transformations of 5-cyano-1-pyrrolines **1** to various heterocycles

Addition of a slight excess of LDA to a solution of 3,4-dihydro-2*H*-pyrrole-2-carbonitriles **1** provides Li-salts **9** which were reacted with several α-bromo-ω-chloroalkanes **10** to provide the respective 5-cyano-5-(ω-chloroalkyl)-1-pyrrolines **11**. These can be transformed to the bicyclic structures **8** by reaction with additional LDA *in situ* (Scheme 2). α-Bromo-ω-chloroalkanes **10** were employed, exploiting the different

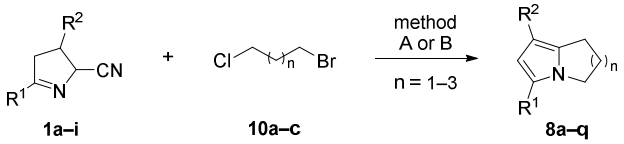
reactivities of the respective leaving group, since it was anticipated that side reactions like dimerization would occur if the respective dichloro- or dibromocompounds were used (*vide infra*).



Scheme 2. Proposed reaction course in the synthesis of compounds **8**

Since 5-alkyl-5-cyano-1-pyrrolines react to pyrroles in the presence of LDA (weaker bases like KHMDS are unsuitable),[53] the annulation step might well proceed via the intermediate 1*H*-pyrroles **12** which thereupon react in a nucleophilic *Exo-Tet* cyclization. This hypothesis is supported by LC-MS-data indicating the intermediate occurrence of compound **12** during the course of the reaction. Using this simple annulation strategy, various 2,4-disubstituted pyrroles fused to saturated 5-, 6- and 7-membered rings could be obtained (Table 1).

Table 1. Synthesis of heterobicycles **8a–q**[a]



Entry	Pyrroline	R^1	R^2	n	Method	t (h)	Product	Yield (%)

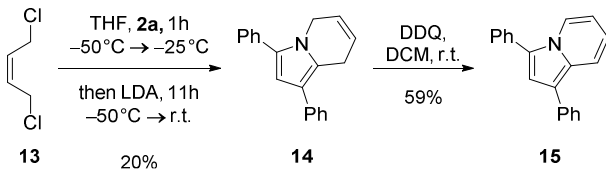
1	**1a**	Ph	Ph	2	A	2	**8a**	88
2	**1a**	Ph	Ph	2	B	2	**8a**	52
3	**1a**	Ph	Ph	1	A	2	**8b**	97
4	**1a**	Ph	Ph	3	A	19	**8c**	55
5	**1b**	Ph	4-CN–C_6H_4	2	A	1	**8d**	88
6	**1b**	Ph	4-CN–C_6H_4	1	A	1	**8e**	88
7	**1b**	Ph	4-CN–C_6H_4	3	A	20	**8f**	53
8	**1c**	Ph	2,3-Cl–C_6H_3	2	A	2	**8g**	79
9	**1c**	Ph	2,3-Cl–C_6H_3	1	A	2	**8h**	82
10	**1d**	2-Naph	Ph	2	A	2	**8i**	71
11	**1d**	2-Naph	Ph	1	A	2	**8j**	84
12	**1e**	2-Naph	2-Br–C_6H_4	2	A	2.5	**8k**	79
13	**1e**	2-Naph	2-Br–C_6H_4	1	A	2.5	**8l**	83
14	**1f**	4-F–C_6H_4	2-Cl–C_6H_4	2	A	1	**8m**	76
15	**1f**	4-F–C_6H_4	2-Cl–C_6H_4	1	A	1	**8n**	74
16	**1g**	4-F–C_6H_4	4-OMe–C_6H_4	2	A	1	**8o**	82
17	**1g**	4-F–C_6H_4	4-OMe–C_6H_4	1	A	1	**8p**	73
18	**1h**	Me	Ph	2	A	2	**8q**	17
19	**1i**	4-Cl–C_6H_4	3-NO_2–C_6H_4	1,2,3	A	-	**-**	-

[a]Reaction conditions: method A: cyanopyrroline **1** (0.5 mmol), THF (10 mL), LDA (0.6 mmol), alkylhalide **10** (0.6 mmol), −78 °C → rt, 1 h, then LDA (1.2 mmol), −78 °C → rt, reaction time stated in the table; method B: cyanopyrroline **1** (0.5 mmol), THF (10 mL), LDA (1.8 mmol), alkylhalide **10** (0.6 mmol), −78 °C → rt, 2 h; [c]a complex reaction mixture was obtained; no desired product or intermediate could be observed.

The reactions leading to 5- or 6-membered fused rings generally proceeded smoothly with high to excellent yields when α-bromo-ω-chloroalkanes were used as electrophiles. For the annulation reactions providing 7-membered rings, i.e. 6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepines, the obtained yields were slightly lower but still satisfactory (entries 4 and 7). It is beneficial to execute these reactions in a stepwise manner (method A) since lower yields were encountered for the synthesis of **8a** by only a single addition of LDA at the beginning of the reaction (method B, 88% vs. 52% yield; entries 1

and 2). Likewise, lower yields and large amounts of byproducts were found when 1,4-dichlorobutane (21% yield) as well as 1,4-dibromobutane (27% yield, determined by ^{1}H NMR) were applied as electrophile. We assume that the lower leaving group tendency of chloride and the resulting higher activation energy needed for the C-alkylation step promotes side reactions of intermediate anion **9** when 1,4-dichlorobutane was used. In contrast to bromide **10a**, the electrophilic reactivity of 1,4-dichlorobutane should not differ significantly from intermediate **11a** which can also lead to undesired dimerization reactions. LC-MS data obtained during the reaction supports this assumption. The latter consideration similarly applies to the reactions employing 1,4-dibromobutane and significant amounts of byproducts resulting from dimerization (21%) along with 2-(but-3-en-1-yl)-3,5-diphenyl-1*H*-pyrrole (21%) resulting from HBr-elimination from intermediate **11a** could be isolated. When the general reaction conditions were applied to pyrroline **1h** carrying an aliphatic substituent R^1, the yield was notably lower (17%) than for the aryl-substituted cyanopyrrolines (entry 18). It is however unclear if this is due to the presence of an additional CH-acidic moiety in the starting material **1h** or intermediate **11h**, respectively, or to a lower stability of product **8q** towards oxidation or polymerization reactions. Interestingly, no successful annulation could be observed when cyanopyrrolines carrying a nitroaryl substituent were employed in the reaction (**1i** entry 19). We hypothesize that in this case the alkylation step fails due to an intermolecular addition of anion **9** to the nitroaromatic ring of a second cyanopyrroline-molecule since we could observe compounds of the corresponding mass by LC-MS.

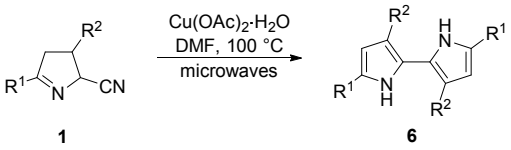
Inspired by these results, the annulation was extended to the preparation of indolizines by employing commercially available (*Z*)-1,4-dichlorobut-2-ene (**13**) as an electrophile to yield 5,8-dihydroindolizine intermediates. To avoid side reactions such as dimerizations (vide supra), the reaction conditions were modified. The lithium salt **9a**, prepared in solution by previously deprotonating **1a** with LDA, was added to a solution of **13**, thus providing a permanent excess of the electrophile. In this fashion, we were able to isolate the corresponding 1,3-diphenyl-5,8-dihydroindolizine (**14**) in 20% yield. The following oxidation with DDQ afforded 1,3-diphenylindolizine (**15**) but the sequence suffered from low efficiency and poor reproducibility (Scheme 3).



Scheme 3: Synthesis of 1,3-diphenylindolizine **15** via 1,3-diphenyl-5,8-dihydroindolizine **14**

When cyanopyrroline **1a** was treated with $Cu(OAc)_2$ in DMF at 100 °C, 2,2'-1*H*,1'*H*-bipyrrole **6a** was obtained in 49% yield (Table 2, entry 1). This reaction also produced pyrrole-2-carbonitrile **3a**, the structure of which was elucidated by NMR. Unfortunately, all attempts to increase the yield of bipyrrole **6** failed. Replacing $Cu(OAc)_2$ with $CuSO_4$, $Cu(OTf)_2$, or $CuCl_2$ did not yield the desired dimerization product which also could not be obtained using other oxidants $FeCl_3$, $Mn(OAc)_3$, I_2, or PIFA. When the previously found reaction conditions were applied to cyanopyrroline **1c**, bipyrrole **6c** was obtained in 10% yield along with the corresponding pyrrole-2-carbonitrile **3c** (40% yield, entry 3).

Table 2. Synthesis of 2,2'-Bipyrroles

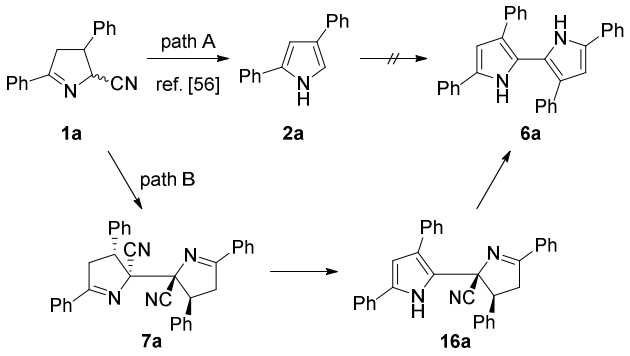


1 6

Entry	R^1	R^2	Product	Yield (%)
1	Ph	Ph	**6a**	49
2	2-Naph	Ph	**6b**	31[a]
3	4-Cl–C_6H_4	3-NO_2–C_6H_4	**6c**	10[b]

[a] Anhydrous copper(II) acetate was used. [b] Pyrrole-2-carbonitrile **3c** was isolated in 40% yield.

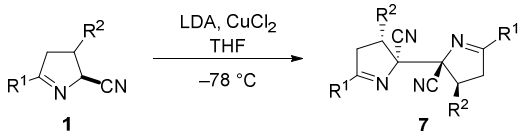
To examine whether bipyrrole formation proceeds through the pyrrole stage (path A) or through a pyrroline dimer (Path B, Scheme 4), pyrrole **2a** (prepared by thermal dehydrocyanation of cyanopyrroline **1a**)[56] was subjected to identical conditions and no bipyrrole **6a** was detected. However, intermediates **7a** and **16a** were detected by LC-MS, so that path A can be ruled out and the reaction most probably proceeds through path B.



Scheme 4. Possible reaction pathways for the synthesis of bipyrroles **6**

Bis(cyanopyrroline) **7a** could be prepared by a different route. Cyanopyrroline **1a** was deprotonated by LDA in THF at –78 °C and treated with $CuCl_2$ (1.20 equiv) to furnish dimerized cyanopyrroline **7a** as a major diastereomer in 59% yield. The total yield of homocoupled cyanopyrrolines was 83% From the ^{1}H NMR spectrum of the crude reaction mixture, the diastereomeric purity[57] of the major diastereoisomer **7a** was calculated as 71% (Table 3, entry 1). The relative configuration of the major diastereomer **7a** was unambiguously determined by X-ray crystallography (see Supporting Information).

Table 3. Diastereoselective Homocoupling of Cyanopyrroline **1**

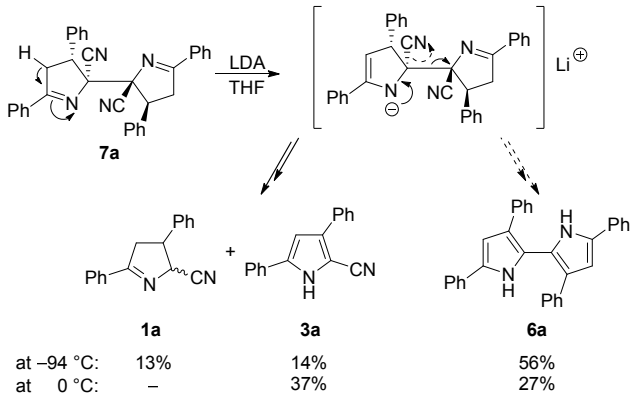


Entry	R^1	R^2	Product	*dp(%)*[a]	Yield (%)[b]
1	Ph	Ph	**7a**	71	59 (83)
2	2-Naph	Ph	**7b**	>84	54 (62)
3	Ph	4-CN–C_6H_4	**7c**	74	33 (47)
4	4-F–C_6H_4	4-MeO–C_6H_4	**7d**	>71	62 (81)

[a] *dp*:diastereomeric purity was calculated by integrating the H-3 signals of the major diastereomer relative to all diastereomers. [b] Isolated yield of major diastereomer. Total yield of dimerized product calculated from the formula: (isolated yield of the major diastereomer) / (dp of the major diastereomer) ×100 is given in parentheses.

Furthermore, deprotonation of the dimerized cyanopyrroline **7a** with LDA at –78 °C in THF gave a mixture of bipyrrole **6a**, pyrrole-2-carbonitrile **3a**, and cyanopyrroline **1a**. Clearly, two competing reactions exist under these conditions (Scheme 5). In addition to

the base-induced double dehydrocyanation, cyanopyrroline **1a** and pyrrole-2-carbonitrile **3a** can be formed by a cleavage of the central C2–C2' bond.



Scheme 5. Reaction of compound **7a** with LDA

The latter process possibly accounts for the limited efficiency of bipyrrole formation. While the reaction of bis(cyanopyrroline) **7a** with LDA in THF at –94 °C gave bipyrrole **6a** as a major product in 56% yield (determined by ^{1}H NMR using an internal standard), this figure decreased to 27% at 0 °C under otherwise identical reaction conditions.

Conclusion

A simple, high yielding method for the one-pot synthesis of 1,3-disubstituted 5,6,7,8-tetrahydroindolizines, 5,7-disubstituted 2,3-dihydro-1*H*-pyrrolizines as well as 1,3-disubstituted 6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepines has been developed. The readily available 3,4-dihydro-2*H*-pyrrole-2-carbonitriles serve as intermediates in all cases. Moreover, the exposure of 3,4-dihydro-2*H*-pyrrole-2-carbonitriles to copper(II) acetate provides a convenient access to bis(cyanopyrrolines) by dimerization or to 2,2'-bipyrroles by subsequent double dehydrocyanation.

Experimental Section

General Methods

All reactions described were carried out under an inert atmosphere of argon in flame- or oven dried glassware. The stated reaction temperatures refer to the temperature of the respective cooling bath. All reagents were reagent grade and used without further purification unless otherwise noted. LDA was purchased in solution from a commercial supplier and titrated against *N*-benzylbenzamide prior to use.[58] Cyanopyrrolines **1a–g** were synthesized as previously reported.[52,53,56] Melting points were determined in open capillary tubes using an electronic apparatus. NMR spectra were recorded on a 400 MHz spectrometer equipped with a 5 mm BBFO probe head with z-gradient and ATM capability. Chemical shifts were referenced to the deuterated solvent (e.g., for $CDCl_3$, δ = 7.26 ppm and 77.16 ppm, for DMSO-d_6, δ = 2.50 ppm and 39.52 ppm for ^1H and ^{13}C NMR, respectively) and reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS, δ = 0.00 ppm).[59] Coupling constants (*J*) are stated in Hz using the splitting abbreviations: s, singlet; d, doublet; t, triplet; quin., quintet; m, multiplet; br, broad. Standard pulse sequences were used for the 2D experiments. FT-Infrared spectra were recorded using a diamond ATR unit. High-resolution mass spectrometry was executed on a QToF-Instrument with a dual electrospray source and a suitable external calibrant. Thin-layer chromatography (TLC) was performed on 0.25 mm silica gel plates ($60F_{254}$) visualizing with UV-light and developing with an anisaldehyde solution (4.1 mL of *p*-anisaldehyde, 1.7 mL AcOH and 5.6 mL H_2SO_4 in 450 mL EtOH) or potassium permanganate solution (2.0 g $KMnO_4$ and 5.5 g $NaCO_3$ in 250 mL H_2O). Flash chromatography was carried out using the indicated solvent system on 35–70 µm silica gel.

General procedure for the microwave synthesis of 2,2'-bipyrroles 6. A 10 mL microwave vessel was charged with cyanopyrroline **1** (1.00 equiv) and a stir bar. The starting material was dissolved in DMF (4.00 mL/ 1 mmol **1**) and $Cu(OAc)_2 \cdot H_2O$ (3.00 equiv) was added. The reaction mixture was heated to 100 °C (microwave irradiation, 150 W) for 15 min. The solution was diluted with ethyl acetate and filtered through a pad of celite. The crude product was purified by a column chromatography.

3,3',5,5'-Tetraphenyl-1*H*,1'*H*-2,2'-bipyrrole (6a). The title compound was prepared according to the general procedure described above from cyanopyrroline **1a** (246 mg, 1.000 mmol) and $Cu(OAc)_2 \cdot H_2O$ (599 mg, 3.000 mmol). The crude product was purified by column chromatography (SiO_2, Cy/EtOAc 10:1) to obtain bipyrrole **6a** (107 mg, 0.245 mmol, 49%) as a colorless foam: R_f = 0.73 (SiO_2, Cy/EtOAc 5:1); ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ (ppm) = 11.71 (d, J = 2.6 Hz, 2H, H-1), 7.81–7.79 (m, 4H, H-2'',6''), 7.38–7.31 (m, 8H, H-3'',5'', H-2',6'), 7.20–7.12 (m, 6H, H-4'', H-3',5'), 7.07 (d, J = 2.6 Hz, 2H, H-4), 7.02–6.98 (m, 2H, H-4'); ^{13}C NMR, HSQC, HMBC (100.6 MHz, DMSO-d_6) δ (ppm) = 136.1 (2C, C-1'), 132.6 (2C, C-1''), 131.9 (2C, C-5), 128.9 (4C, C-3'',5''), 128.4 (4C, C-3',5'), 126.0 (2C, C-4''), 125.8 (4C, C-2',6'), 125.2 (2C, C-4'), 124.7 (2C, C-3), 123.8 (4C, C-2'',6''), 121.7 (2C, C-2), 105.5 (2C, C-4) ppm; IR (ATR): ν (cm^{-1}) = 3412, 3060, 3025, 2957, 2924, 2855, 1723, 1602, 1490, 1462, 1278, 1025, 758, 694; ESI-HRMS calcd for $[C_{32}H_{24}N_2]^+$ 436.1939, found 436.1932.

5,5'-Di(naphthalen-2-yl)-3,3'-diphenyl-1*H*,1'*H*-2,2'-bipyrrole (6b). The title compound was prepared according to the general procedure described above from cyanopyrroline **1d** (148 mg, 0.500 mmol) and $Cu(OAc)_2$ (272 mg, 1.500 mmol). The crude product was purified by column chromatography (SiO_2, Cy/EtOAc 6:1) to obtain bipyrrole **6b** (42 mg, 0.079 mmol, 31%) as a yellow foam: R_f = 0.39 (SiO_2, Cy/EtOAc 6:1); ^{1}H NMR, COSY

(300 MHz, DMSO-d_6) δ (ppm) = 11.91 (d, J = 2.5 Hz, 2H, N*H*), 8.33 (br s, 2H, H-1''), 8.02 (dd, J = 8.7, 1.7 Hz, 2H, H-3''), 7.92 (d, J = 8.7 Hz, 2H, H-4''), 7.87 (dd, J = 8.0, 1.3 Hz, 2H, H-5''), 7.82 (dd, J = 8.3, 1.2 Hz, 2H, H-8''), 7.49 (ddd, J = 8.3, 6.9, 1.3 Hz, 2H, H-7''), 7.44 (ddd, J = 8.0, 6.9, 1.2 Hz, 2H, H-6''), 7.40–7.37 (m, 4H, H-2',6'), 7.26 (d, J = 2.5 Hz, 2H, H-4), 7.18–7.14 (m, 4H, H-3',5'), 7.04–6.99 (m, 2H, H-4'); ^{13}C NMR, HSQC, HMBC (75.5 MHz, DMSO-d_6) δ (ppm) = 135.8 (2C, C-1'), 133.5 (2C, C-8a''), 131.8 (2C, C-5), 131.5 (2C, C-4a''), 129.8 (2C, C-2''), 128.21 (4C, C-3',5'), 128.15 (2C, C-4''), 127.6 (2C, C-5''), 127.5 (2C, C-8''), 126.5 (2C, C-7''), 125.6 (4C, C-2',6'), 125.2 (2C, C-6''), 125.1 (2C, C-4'), 124.7 (2C, C-3), 123.1 (2C, C-3''), 122.0 (2C, C-2), 120.8 (2C, C-1''), 106.1 (2C, C-4); IR (ATR): ν (cm^{-1}) = 3393, 3055, 2954, 2922, 1628, 1598, 1502, 1160, 799, 765; ESI-HRMS calcd for $[C_{40}H_{28}N_2 + H]^+$ 537.2331, found 537.2323.

5,5'-Bis(4-chlorophenyl)-3,3'-bis(3-nitrophenyl)-1*H*,1'*H*-2,2'-bipyrrole (6c). The title compound was prepared according to the general procedure described above from cyanopyrroline **1i** (162 mg, 0.500 mmol) and $Cu(OAc)_2 \cdot H_2O$ (300 mg, 1.500 mmol). The crude product was purified by column chromatography (SiO_2, Cy/EtOAc 10:1) to obtain bipyrrole **6c** (14 mg, 0.024 mmol, 10%) as a yellow foam: R_f = 0.21 (SiO_2, Cy/EtOAc 10:1); ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ (ppm) = 12.08 (d, J = 2.7 Hz, 2H, N*H*), 7.96 (t, J = 2.0 Hz, 2H, H-2'), 7.90–7.85 (AA' part of AA'–BB' system, 4H, H-2'',6''), 7.80 (ddd, J = 8.2, 2.0, 1.0 Hz, 2H, H-4'), 7.60 (ddd, J = 7.8, 2.0, 1.0 Hz, 2H, H-6'), 7.51–7.44 (BB' part of AA'–BB' system, 4H, H-3'',5''), 7.38 (pseudo-t, $J_{app} \approx$ 8 Hz, 2H, H-5'), 7.25 (d, J = 2.7 Hz, 2H, H-4); ^{13}C NMR, HSQC, HMBC (100.6 MHz, DMSO-d_6) δ (ppm) = 147.7 (2C, C-3'), 137.4 (2C, C-1'), 132.2 (2C, C-6'), 131.8 (2C, C-5), 130.8 (2C, C-1''), 130.6 (2C, C-4''), 129.6 (2C, C-5'), 128.8 (4C, C-3'',5''), 125.5 (4C, C-2'',6''), 122.3 (2C, C-3), 122.0 (2C, C-2), 120.0 (2C, C-2'), 119.8 (2C, C-4'), 106.6 (2C, C-4); IR (ATR):

ν (cm^{-1}) = 3364, 3191, 2954, 2923, 2853, 1648, 1527, 1463, 1347, 1095, 800, 742; ESI-HRMS calcd for $[C_{32}H_{20}N_4O_4Cl_2 + Na]^+$ 617.0759, found 617.0775.

General procedure for the copper(II)-mediated homocoupling of cyanopyrrolines. To a solution of cyanopyrroline **1** (1.00 equiv) in freshly distilled THF (10 mL/ mmol **1**) were added a solution of LDA (1.20 equiv) in THF/heptane/ethylbenzene at –78 °C under argon athmosphere. After stirring 3 min, solid $CuCl_2$ (1.10 equiv) was added in small portions at the same temperature. The reaction mixture was stirred 1–3 h until almost all starting materials were consumed. Then, it was quenched with H_2O (2 mL). The solution was diluted with ethyl acetate (40 mL/mmol **1**) and washed with 0.25 M EDTA (20 mL × 5) solution (pH 10), and brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The diastereomeric ratio was calculated form the ^{1}H NMR spectrum of the crude product by integrating the H-3 proton. Bispyrroline **7** was obtained after recrystallization from proper solvent mixtures.

3,3',5,5'-Tetraphenyl-3,3',4,4'-tetrahydro-2*H*,2'*H*-[2,2'-bipyrrole]-2,2'-dicarbonitrile (7a). The title compound was prepared according to the general procedure described above from cyanopyrroline **1a** (1.231 g, 5.00 mmol), LDA (6.00 mmol), and $CuCl_2$ (739 mg, 5.50 mmol). Recrystallization from hexanes/EtOAc (10:1) provided compound **7a** (720 mg, 1.47 mmol, 59%) as a yellowish solid: mp = 220–221 °C (hexanes/EtOAc); R_f = 0.19 (SiO_2, hexanes/EtOAc 4:1); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.73–7.69 (m, 2H, H-2'',6''), 7.45–7.40 (m, 1H, H-4''), 7.39–7.29 (m, 7H, H-2',6', H-3',5',H-4', H-3'',5''), 4.55 (dd, *J* = 9.2, 2.6 Hz, 1H, H-3), 3.62 (dd, *J* = 18.0, 9.2 Hz, 1H, H-4a), 3.33 (dd, *J* = 18.0, 2.6 Hz, 1H, H-4b); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 181.0 (2C, C-5), 141.1 (2C, C-1'), 132.3 (2C, C-4''), 132.1 (2C, C-1''), 129.2 (4C, C-3',5'), 128.8 (4C, C-3'',5''), 128.3 (2C, C-4'), 128.2 (4C, C-2'',6''), 127.8 (4C,

C-2',6'), 117.0 (2C, CN), 88.6 (2C, C-2), 49.0 (2C, C-3), 45.6 (2C, C-4); IR (ATR): ν (cm^{-1}) = 3063, 3031, 2961, 2926, 2210, 1608, 1575, 1347, 1057, 760, 740; ESI-HRMS calcd for $[C_{34}H_{26}N_4 + H]^+$ 491.2236, found 491.2234.

5,5'-Di(naphthalene-2-yl)-3,3'-diphenyl-3,3',4,4'-tetrahydro-2*H*,2'*H*-[2,2'-bipyrrole]-2,2'-dicarbonitrile (7b). The title compound was prepared according to the general procedure described above from cyanopyrroline **1d** (274 mg, 0.92 mmol), LDA (1.10 mmol), and $CuCl_2$ (137 mg, 1.02 mmol). Recrystallization from hexanes/CH_2Cl_2 (4:1) provided compound **7b** (145 mg, 0.25 mmol, 54%) as yellowish solid: mp = 226–228 °C (hexanes/CH_2Cl_2); R_f = 0.33 (hexanes/EtOAc 2:1); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.98–7.94 (m, 4H, H-1'', H-3''), 7.75–7.70 (m, 4H, H-4'', H-5''), 7.67–7.64 (m, 2H, H-8''), 7.48 (ddd, J = 8.2, 6.9, 1.3 Hz, 2H, H-6''), 7.43–7.32 (m, 12H, H-7'', H-2',6', H-3',5', H-4'), 4.65 (dd, J = 9.2, 2.6 Hz, 2H, H-3), 3.78 (dd, J = 17.8, 9.2 Hz, 2H, H-4a), 3.47 (dd, J = 17.8, 2.6 Hz, 2H, H-4b); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 181.0 (2C, C-5), 141.2 (2C, C-1'), 135.1 (2C, C-4a''), 132.6 (2C, C-8a''), 129.8 (2C, C-1''), 129.6 (2C, C-2''), 129.3 (4C, C-3',5'), 128.9 (2C, C-8''), 128.7 (2C, C-4''), 128.3 (2C, C-4'), 128.1 (2C, C-6''), 127.9 (4C, C-2',6'), 127.8 (2C, C-5''), 126.8 (2C, C-7''), 123.9 (2C, C-3''), 117.1 (2C, CN), 88.7 (2C, C-2), 49.1 (2C, C-3), 45.6 (2C, C-4); IR (ATR): ν (cm^{-1}) = 3060, 3031, 2963, 2926, 2210, 1606, 1594, 1573, 1354, 861, 822, 736; ESI-HRMS calcd for $[C_{42}H_{30}N_4 + Na]^+$ 613.2368, found 613.2370.

3,3'-Bis(4-cyanophenyl-5,5'-diphenyl-3,3',4,4'-tetrahydro-2*H*,2'*H*-[2,2'-bipyrrole]-2,2'-dicarbonitrile (7c). The title compound was prepared according to the general procedure described above from cyanopyrroline **1b** (271 mg, 1.00 mmol), LDA (1.20 mmol), and $CuCl_2$ (148 mg, 1.10 mmol). Recrystallization from hexanes/CH_2Cl_2 (8:1) provided compound **7c** (88 mg, 0.16 mmol, 33%) as yellow solid: mp = 136–138 °C

(hexanes/CH_2Cl_2); R_f = 0.12 (hexanes/EtOAc 6:1); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.71–7.68 (m, 4H, H-2'',6''), 7.68–7.65 (AA' part of AA'–BB' system, 4H, H-3',5'), 7.49–7.43 (m, 2H, H-4''), 7.43–7.39 (BB' part of AA'–BB' system, 4H, H-2',6'), 7.39–7.30 (m, 4H, H-3'',5''), 4.60 (dd, J = 9.2, 2.8 Hz, 2H, H-3), 3.68 (dd, J = 18.2, 9.2 Hz, 2H, H-4a), 3.32 (dd, J = 18.2, 2.8 Hz, 2H, H-4b); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 181.1 (2C, C-5), 145.8 (2C, C-1'), 133.1 (4C, C-3',5'), 132.9 (2C, C-4''), 131.5 (2C, C-1''), 129.0 (4C, C-3'',5''), 128.8 (4C, C-2',6'), 128.2 (4C, C-2'',6''), 118.5 (2C, 4'-CN), 116.6 (2C, 1-CN), 112.5 (2C, C-4'), 87.9 (2C, C-2), 49.0 (2C, C-3), 45.4 (2C, C-4); IR (ATR): ν (cm^{-1}) = 3063, 2960, 2926, 2854, 2230, 1609, 1575, 1449, 1348, 1057, 850, 763; ESI-HRMS calcd for $[C_{36}H_{24}N_6 + H]^+$ 541.2141, found 541.2142.

5,5'-Bis(4-fluorophenyl)-3,3'-bis(4-methoxyphenyl-3,3',4,4'-tetrahydro-2*H*,2'*H*-[2,2'-bipyrrole]-2,2'-dicarbonitrile (7d): The title compound was prepared according to the general procedure described above from cyanopyrroline **1g** (370 mg, 1.26 mmol), LDA (1.51 mmol), and $CuCl_2$ (186 mg, 1.38 mmol). Recrystallization from hexanes/EtOAc (5:1) provided compound **7d** (228 mg, 0.39 mmol, 62%) as colorless solid: mp = 121–122 °C (hexanes/EtOAc); R_f = 0.19 (hexanes/EtOAc 2:1); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.75–7.68 (m, 4H, H-2'',6''), 7.22–7.17 (AA' part of AA'–BB' system, 4H, H-2',6'), 7.05–6.98 (m, 4H, H-3'',5''), 6.90–6.86 (BB' part of AA'–BB' system, 4H, H-3',5'), 4.49 (dd, J = 9.2, 2.8 Hz, 2H, H-3), 3.79 (s, 6H, OCH_3), 3.54 (dd, J = 18.0, 9.2 Hz, 2H, H-4a), 3.25 (dd, J = 18.0, 2.8 Hz, 2H, H-4b); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 179.5 (2C, C-5), 165.3 (d, $^1J_{CF}$ = 253.9 Hz, 2C, C-4''), 159.5 (2C, C-4'), 132.8 (2C, C-1'), 130.4 (d, $^3J_{CF}$ = 8.9 Hz, 4C, C-2'',6''), 128.9 (4C, C-2',6'), 128.5 (d, $^4J_{CF}$ = 3.3 Hz, 2C, C-1''), 117.0 (CN), 116.1 (d, $^2J_{CF}$ = 22.0 Hz, 4C, C-3'',5'') , 114.6 (4C,

C-3',5'), 88.5 (2C, C-2), 55.4 (2C, OCH_3), 48.4 (2C, C-3), 45.6 (2C, C-4); IR (ATR): ν (cm^{-1}) = 3064, 3003, 2960, 2935, 2838, 2211, 1612, 1603, 1585, 1511, 1343, 1250, 1235, 1057, 840, 808, 735; ESI-HRMS calcd for $[C_{36}H_{28}N_4O_2F_2 + Na]^+$ 609.2078, found 609.2083.

General procedure for the synthesis of bicyclic structures 8a–p. The respective cyanopyrroline (**1a–g**) (ca. 0.5 mmol, 1.0 equiv) was dissolved in abs THF (10 mL, 0.05 mol/mL) under an argon atmosphere. The resulting solution was cooled to −78 °C and LDA (1.2 equiv) was added dropwise. The solution was stirred for about 5 min, after which the respective alkyl halide (**10a–c**) (1.2 equiv) was added dropwise. The cooling bath was removed and stirring was continued until LC-MS indicated full conversion of the starting material (usually about 1 h). The solution was again cooled to −78 °C and another portion of LDA (2.4 equiv) was added. After stirring for 5 min at that temperature, the cooling bath was removed and stirring was continued for the time indicated in table 1, at which point LC-MS showed full conversion of the intermediate alkylated cyanopyrroline. The reaction mixture was quenched by addition of water (10 mL) and EtOAc (10 mL), the organic layer was washed with water (10 mL) then brine (10 mL) and the combined aqueous layers were extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried over sodium sulfate, concentrated under reduced pressure and the crude product was purified by silica gel column chromatography.

1,3-Diphenyl-5,6,7,8-tetrahydroindolizine (8a). Method A: The title compound was prepared according to the general procedure from cyanopyrroline **1a** (0.123 g, 0.499 mmol, 1.0 equiv) and 1-bromo-4-chlorobutane (0.07 mL, 0.60 mmol, 1.2 equiv) using LDA (0.60 mmol, 1.2 equiv for the alkylation step, then 1.20 mmol, 2.4 equiv for

the annulation step). Purification by column chromatography (SiO_2, hexanes/Et_2O (250:1→100:1) yielded **8a** (120 mg, 0.439 mmol, 88%) as a colorless solid: mp 111–112 °C (hexanes/Et_2O); R_f = 0.28 (SiO_2, hexanes/Et_2O 150:1); ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ (ppm) = 7.48–7.39 (m, 6H, H_{Ph}-2,6, $H_{Ph'}$-2,6, $H_{Ph'}$-3,5), 7.36–7.32 (m, 2H, H_{Ph}-3,5), 7.32–7.27 (m, 1H, $H_{Ph'}$-4), 7.17–7.12 (m, 1H, H_{Ph}-4), 6.41 (s, 1H, H-2), 3.96 (t, J = 5.9 Hz, 2H, H-5), 2.95 (t, J = 6.3 Hz, 2H, H-8), 1.91–1.85 (m, 2H, H-6), 1.84–1.77 (m, 2H, H-7); ^{13}C NMR, HSQC, HMBC (100.6 MHz, DMSO-d_6) δ (ppm) = 136.6 (C_{Ph}-1), 132.9 ($C_{Ph'}$-1), 132.1 (C-3), 128.5 ($C_{Ph'}$-2,6), 128.4 (C_{Ph}-3,5), 128.2 ($C_{Ph'}$-3,5), 126.9 (C-8a), 126.6 (C_{Ph}-2,6), 126.4 ($C_{Ph'}$-4), 124.6 (C_{Ph}-4), 119.1 (C-1), 107.6 (C-2), 44.7 (C-5), 23.8 (C-8), 23.1 (C-6), 20.4 (C-7); IR (ATR): ν (cm^{-1}) = 3053, 2930, 1602, 1560, 1490, 1451, 1327, 1169, 759, 698; ESI-HRMS calcd for $[C_{20}H_{19}N + H]^+$ 274.1596, found 274.1593. – **Method B:** The title compound was prepared by a single addition of LDA (1.81 mmol, 3.6 equiv) to a solution of cyanopyrroline **1a** (0.124 g, 0.503 mmol, 1.0 equiv) in abs THF (10 mL) at −78 °C, followed by the addition of 1-bromo-4-chlorobutane (0.07 mL, 0.60 mmol, 1.2 equiv). The cooling bath was removed and the mixture stirred for a further 2 h, at which point LC-MS indicated full conversion. Workup was carried out as described above to yield **8a** (71 mg, 0.260 mmol, 52%) as a colorless solid. The analytical data were in agreement with the abovementioned.

5,7-Diphenyl-2,3-dihydro-1*H*-pyrrolizine (8b). The title compound was prepared according to the general procedure from cyanopyrroline **1a** (0.123 g, 0.499 mmol, 1.0 equiv) and 1-bromo-3-chloropropane (0.06 mL, 0.60 mmol, 1.2 equiv) using LDA (0.60 mmol, 1.2 equiv for the alkylation step, then 1.20 mmol, 2.4 equiv for the annulation step). Purification by column chromatography (SiO_2, hexanes/Et_2O 100:1) yielded **8b** (126 mg, 0.486 mmol, 97%) as a light yellow solid: mp 148–

149 °C (hexanes/Et_2O); R_f = 0.23 (SiO_2, hexanes/Et_2O 150:1); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.56–7.51 (m, 4H, H_{Ph}-2,6, $H_{Ph'}$-2,6), 7.43–7.39 (m, 2H, H_{Ph}-3,5), 7.39–7.34 (m, 2H, $H_{Ph'}$-3,5), 7.28–7.22 (m, 1H, H_{Ph}-4), 7.20–7.14 (m, 1H, $H_{Ph'}$-4), 6.74 (s, 1H, H-6), 4.18 (t, J = 7.1 Hz, 2H, H-3), 3.15 (t, J = 7.3 Hz, 2H, H-1), 2.61 (pseudo-quin., $J \approx 7$ Hz, 2H, H-2); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 136.5 ($C_{Ph'}$-1), 136.0 (C-7a), 133.5 (C_{Ph}-1), 129.4(C-5), 128.8, 128.7 (2C, C_{Ph}-3,5, $C_{Ph'}$-3,5), 126.1 (C_{Ph}-4), 125.9 (C_{Ph}-2,6), 125.3 ($C_{Ph'}$-2,6), 124.8 ($C_{Ph'}$-4), 116.3 (C-7), 108.8 (C-6), 46.8 (C-3), 28.1 (C-2), 25.5 (C-1); IR (ATR): ν (cm^{-1}) = 3032, 2954, 1602, 1492, 1455, 1391, 1298, 1144, 754, 694; ESI-HRMS calcd for $[C_{19}H_{17}N + H]^+$ 260.1439, found 260.1439. The spectroscopic data are in accordance to the literature.[42]

1,3-Diphenyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine (8c). The title compound was prepared according to the general procedure from cyanopyrroline **1a** (0.128 g, 0.520 mmol, 1.0 equiv) and 1-bromo-5-chloropentane (0.08 mL, 0.60 mmol, 1.2 equiv) using LDA (0.60 mmol, 1.2 equiv for the alkylation step, then 1.20 mmol, 2.4 equiv for the annulation step). Purification by column chromatography (SiO_2, hexanes/Et_2O 150:1) yielded **8c** (82 mg, 0.285 mmol, 55%) as a colorless solid: mp 131–132 °C (hexanes/Et_2O); R_f = 0.34 (SiO_2, hexanes/Et_2O 150:1); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.46–7.38 (m, 8H, H_{Ph}-2,6, H_{Ph}-3,5, $H_{Ph'}$-2,6, $H_{Ph'}$-3,5), 7.35–7.30 (m, 1H, H_{Ph}-4), 7.27–7.22 (m, 1H, H_{Ph}-4), 6.27 (s, 1H, H-2), 4.09–3.98 (m, 2H, H-5), 3.06–2.93 (m, 2H, H-9), 1.98–1.69 (m, 6H, H-6,7,8); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 137.6 (Cq_{Ph}), 133.8 (Cq_{Ph}), 133.6 (C-3), 133.4(C-9a), 129.3 (CH_{Ph}), 128.7 (CH_{Ph}), 128.5 (CH_{Ph}), 128.4 (CH_{Ph}), 126.7 (Cq_{Ph}), 125.4 (Cq_{Ph}), 121.6 (C-1), 108.1 (C-2), 46.6 (C-5), 31.2 (C-7), 29.7 (C-6), 28.0 (C-8), 26.0 (C-9); IR (ATR): ν (cm^{-1}) = 3029, 2924, 1602, 1490, 1445, 1394, 1344, 909, 757, 699; ESI-HRMS calcd

for $[C_{21}H_{21}N + H]^+$ 288.1752, found 288.1744. The spectroscopic data are in accordance to the literature.[60]

4-(3-Phenyl-5,6,7,8-tetrahydroindolizin-1-yl)benzonitrile (8d). The title compound was prepared according to the general procedure from cyanopyrroline **1b** (0.136 g, 0.501 mmol, 1.0 equiv) and 1-bromo-4-chlorobutane (0.07 mL, 0.60 mmol, 1.2 equiv) using LDA (0.60 mmol, 1.2 equiv for the alkylation step, then 1.20 mmol, 2.4 equiv for the annulation step). Purification by column chromatography (SiO_2, Cy/EtOAc 15:1) yielded **8d** (131 mg, 0.439 mmol, 88%) as a colorless solid: mp 128.5–129.5 °C (Cy/EtOAc); R_f = 0.26 (SiO_2, Cy/EtOAc 15:1); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.64–7.60 (AA' part of AA'–BB' system, 2H, H-3',5'), 7.56–7.51 (BB' part of AA'–BB' system, 2H, H-2',6'), 7.44–7.39 (m, 4H, H-2'',6'', H-3'',5''), 7.36–7.31 (m, 1H, H-4''), 6.45 (s, 1H, H-2), 3.98 (t, J = 5.8 Hz, 2H, H-5), 3.05 (t, J = 6.3 Hz, 2H, H-8), 2.01–1.93 (m, 2H, H-6), 1.93–1.88 (m, 2H, H-7); ^{13}C NMR, HSQC, HMBC (100.6 MHz, DMSO-d_6) δ (ppm) = 141.8 (C-1'), 134.0 (C-3), 132.9 (C-1''), 132.4 (C-3',5'), 129.0 (C-2'',6''), 128.7 (C-8a), 128.6 (C-*3'',5''*), 127.3 (C-4''), 127.1 (C-2',6'), 119.8 (*C*N), 118.6 (C-1), 107.8 (C-2), 107.7 (C-4'), 45.3 (C-5), 24.6 (C-8), 23.5 (C-6), 20.9 (C-7); IR (ATR): ν (cm^{-1}) = 2945, 2864, 2221, 1602, 1526, 1327, 1174, 842, 763, 700; ESI-HRMS calcd for $[C_{21}H_{18}N_2 + H]^+$ 299.1548, found 299.1535.

4-(5-Phenyl-2,3-dihydro-1*H*-pyrrolizin-7-yl)benzonitrile (8e). The title compound was prepared according to the general procedure from cyanopyrroline **1b** (0.136 g, 0.501 mmol, 1.0 equiv) and 1-bromo-3-chloropropane (0.06 mL, 0.60 mmol, 1.2 equiv) using LDA (0.60 mmol, 1.2 equiv for the alkylation step, then 1.20 mmol, 2.4 equiv for the annulation step). Purification by column chromatography (SiO_2, Cy/EtOAc 10:1) yielded **8e** (126 mg, 0.443 mmol, 88%) as a colorless solid: mp 217–219 °C (Cy/EtOAc);

R_f = 0.20 (SiO_2, Cy/EtOAc 10:1); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.63–7.59 (AA' part of AA'–BB' system, 2H, H-3'',5''), 7.57–7.54 (BB' part of AA'–BB' system, 2H, H-2'',6''), 7.52–7.48 (m, 2H, H-2',6'), 7.43–7.37 (m, 2H, H-3',5'), 7.29–7.24 (m, 1H, H-4'), 6.71 (s, 1H, H-6), 4.19 (t, J = 7.1 Hz, 2H, H-3), 3.15 (t, J = 7.4 Hz, 2H, H-1), 2.65 (pseudo-quin., $J \approx 7$ Hz , 2H, H-2); ^{13}C NMR, HSQC, HMBC (100.6 MHz, DMSO-d_6) δ (ppm) = 141.0 (C-1''), 137.6 (C-7a), 132.7 (C-1'), 132.5 (C-3'',5''), 130.2 (C-5), 128.8 (C-3',5'), 126.5 (C-4'), 125.9 (C-2',6'), 125.0 (C-2'',6''), 119.7 (CN), 114.6 (C-7), 108.5 (C-6), 107.2 (C-4''), 46.7 (C-3), 27.8 (C-2), 25.7 (C-1); IR (ATR): ν (cm^{-1}) = 2941, 2854, 2221, 1599, 1524, 1300, 1179, 846, 767, 698; ESI-HRMS calcd for $[C_{20}H_{16}N_2 + H]^+$ 285.1392, found 285.1393.

4-(3-Phenyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-1-yl)benzonitrile (8f). The title compound was prepared according to the general procedure from cyanopyrroline **1b** (0.139 g, 0.512 mmol, 1.0 equiv) and 1-bromo-5-chloropentane (0.08 mL, 0.60 mmol, 1.2 equiv) using LDA (0.60 mmol, 1.2 equiv for the alkylation step, then 1.20 mmol, 2.4 equiv for the annulation step). Purification by column chromatography (SiO_2, Cy/EtOAc 30:1) yielded **8f** (85 mg, 0.272 mmol, 53%) as a light yellow solid: mp 155–156 °C (Cy/EtOAc); R_f = 0.30 (SiO_2, Cy/EtOAc 20:1); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.66–7.61 (AA' part of AA'–BB' system, 2H, H-3',5'), 7.48–7.43 (BB' part of AA'–BB' system, 2H, H-2',6'), 7.43–7.40 (m, 2H, H-3'',5''), 7.37–7.31 (m, 3H, H-2'',6'', H-4''), 6.22 (s, 1H, H-2), 4.04–4.00 (m, 2H, H-5), 2.95–2.91 (m, 2H, H-9), 1.92–1.85 (m, 2H, H-7), 1.85–1.74 (m, 4H, H-6, H-8); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 142.6 (C-1'), 134.4 (2C, C-3, C-9a), 133.2 (C-1''), 132.3 (C-3',5'), 129.3 (C-2'',6''), 128.8, 128.6 (4C, C-2',6', C-3'',5''), 127.2 (C-4''), 120.1 (C-1),119,7 (CN) 108,4 (C-4'), 107.8 (C-2), 46.6 (C-5), 31.1 (C-7), 29.5 (C-6), 27.6 (C-8), 26.0 (C-9); IR

(ATR): ν (cm^{-1}) = 2925, 2851, 2223, 1603, 1346, 910, 844, 761, 731, 702; ESI-HRMS calcd for $[C_{22}H_{20}N_2 + Na]^+$ 335.1524, found 335.1518.

1-(2,3-Dichlorophenyl)-3-phenyl-5,6,7,8-tetrahydroindolizine (8g). The title compound was prepared according to the general procedure from cyanopyrroline **1c** (0.158 g, 0.501 mmol, 1.0 equiv) and 1-bromo-4-chlorobutane (0.07 mL, 0.60 mmol, 1.2 equiv) using LDA (0.60 mmol, 1.2 equiv for the alkylation step, then 1.20 mmol, 2.4 equiv for the annulation step). Purification by column chromatography (SiO_2, hexanes/Et_2O 150:1→100:1) yielded **8g** (135 mg, 0.394 mmol, 79%) as a colorless solid: mp 151–152 °C (hexanes/Et_2O); R_f = 0.28 (SiO_2, hexanes/Et_2O 100:1); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.48–7.44 (m, 2H, H-2'',6''), 7.42–7.37 (m, 2H, H-3'',5''), 7.36 (dd_{app}, J_{app} = 7.8, 1.7 Hz, 1H, H-4'), 7.31–7.25 (m, 2H, H-4'', H-6'), 7.17 (t_{app}, J_{app} = 7.8, 1H, H-5'), 6.37 (s, 1H, H-2), 4.02 (t, J = 6.0 Hz, 2H, H-5), 2.79 (t, J = 6.4 Hz, 2H, H-8), 2.00–1.94 (m, 2H, H-6), 1.88–1.81 (m, 2H, H-7); ^{13}C NMR, HSQC, HMBC (100.6 MHz, DMSO-d_6) δ (ppm) = 138.2 (C-1'), 133.5 (C-3'), 133.3 (C-1'') 132.4 (C-3), 131.9 ((C-2'), 130.2 (C-6'), 128.9 (C-2'',6''), 128.6 (C-8a), 128.5 (C-3'',5''), 128.2 (C-4'), 126,7 (2C, C-5', C-4''), 117.9 (C-1), 110.0 (C-2), 45.1 (C-5), 24.0 (C-6), 23.6 (C-8), 20.9 (C-7); IR (ATR): ν (cm^{-1}) = 2948, 2861, 1601, 1582, 1446, 1403, 1326, 1030, 760, 698; ESI-HRMS calcd for $[C_{20}H_{17}NCl_2 + H]^+$ 342.0816, found 342.0813.

7-(2,3-Dichlorophenyl)-5-phenyl-2,3-dihydro-1*H*-pyrrolizine (8h). The title compound was prepared according to the general procedure from cyanopyrroline **1c** (0.158 g, 0.501 mmol, 1.0 equiv) and 1-bromo-3-chloropropane (0.06 mL, 0.60 mmol, 1.2 equiv) using LDA (0.60 mmol, 1.2 equiv for the alkylation step, then 1.20 mmol, 2.4 equiv for the annulation step). Purification by column chromatography (SiO_2, hexanes/Et_2O 150:1) yielded **8h** (135 mg, 0.411 mmol, 82%) as a colorless oil, which solidified after storing

for several days at −25 °C: mp 104–106 °C (hexanes/Et_2O); R_f = 0.35 (SiO_2, hexanes/Et_2O 100:1); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.53–7.50 (m, 2H, H-2',6'), 7.41–7.36 (m, 2H, H-3',5'), 7.35–7.30 (m, 2H, H-4'', H-6''), 7.25–7.21 (m, 1H, H-4'). 7.18 (t_{app}, J_{app} = 7.8, 1H, H-5''), 6.65 (s, 1H, H-6), 4.21 (t, J = 7.0 Hz, 2H, H-3), 2.97 (t, J = 7.4 Hz, 2H, H-1), 2.57 (pseudo-quin., $J \approx 7$ Hz, 2H, H-2); ^{13}C NMR, HSQC, HMBC (100.6 MHz, DMSO-*d*$_6$) δ (ppm) = 138.0 (C-3''), 137.8 (C-7a), 133.7 (C-2''), 133.3 (C-1'), 130.6 (C-1''), 129.2 (C-6''), 128.8 (3C, C-5, C-3',5'), 127.8 (C-4''), 127.0 (C-5''), 126,2 (C-4'), 125.9 (C-2',6'), 114.3 (C-7), 112.0 (C-6), 47.2 (C-3), 28.2 (C-2), 25.6 (C-1); IR (ATR): ν (cm^{-1}) = 2976, 2879, 1603, 1584, 1451, 1402, 1298, 1137, 758, 695; ESI-HRMS calcd for $[C_{19}H_{15}NCl_2 + H]^+$ 328.0660, found 328.0670.

3-(Naphthalen-2-yl)-1-phenyl-5,6,7,8-tetrahydroindolizine (8i). The title compound was prepared according to the general procedure from cyanopyrroline **1d** (0.148 g, 0.499 mmol, 1.0 equiv) and 1-bromo-4-chlorobutane (0.07 mL, 0.60 mmol, 1.2 equiv) using LDA (0.60 mmol, 1.2 equiv for the alkylation step, then 1.20 mmol, 2.4 equiv for the annulation step). Purification by column chromatography (SiO_2, hexanes/Et_2O 150:1→100:1) yielded **8i** (115 mg, 0.356 mmol, 71%) as a colorless solid: mp 167–169 °C (hexanes/Et_2O); R_f = 0.20 (SiO_2, hexanes/Et_2O 100:1); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.90–7.82 (m, 4H, H_{Naph}), 7.61 (dd_{app}, J_{app} = 8.5, 1.8 Hz, 1H, H_{Naph}), 7.53–7.44 (m, 4H, 2',6'-*H*, 2 × H_{Naph}), 7.41–7.35 (m, 2H, H-3',5'), 7.23–7.17 (m, 1H, H-4'), 6.56 (s, 1H, H-2), 4.09 (t, J = 5.9 Hz, 2H, H-5), 3.09 (t, J = 6.4 Hz, 2H, H-8), 2.02–1.96 (m, 2H, H-6), 1.95–1.87 (m, 2H, H-7); ^{13}C NMR, HSQC, HMBC (100.6 MHz, DMSO-*d*$_6$) δ (ppm) = 136.8 (C-1'), 133.4 (Cq_{Naph}), 133.0 (C-3), 132.1 (Cq_{Naph}), 130.8 (Cq_{Naph}), 128.4 (C-3',5'), 127.9 (2C, CH_{Naph}), 127.7 (CH_{Naph}), 127.5 (C-8a), 127.3 (3C, C-2',6', CH_{Naph}), f127.0 (CH_{Naph}), 126.3 (CH_{Naph}), 125.8 (CH_{Naph}), 125,0 (C-4'), 120.3

(C-1), 108.6 (C-2), 45.3 (C-5), 24.1 (C-8), 23.7 (C-6), 21.0 (C-7); IR (ATR): ν (cm^{-1}) = 3053, 2943, 1628, 1601, 1449, 1327, 1170, 908, 762, 698; ESI-HRMS calcd for $[C_{24}H_{21}N + H]^+$ 324.1752, found 324.1763.

5-(Naphthalen-2-yl)-7-phenyl-2,3-dihydro-1*H*-pyrrolizine (8j). The title compound was prepared according to the general procedure from cyanopyrroline **1d** (0.148 g, 0.499 mmol, 1.0 equiv) and 1-bromo-3-chloropropane (0.06 mL, 0.60 mmol, 1.2 equiv) using LDA (0.60 mmol, 1.2 equiv for the alkylation step, then 1.20 mmol, 2.4 equiv for the annulation step). Purification by column chromatography (SiO_2, hexanes/Et_2O 150:1) yielded **8j** (130 mg, 0.420 mmol, 84%) as a colorless solid: mp 153.5–154.5 °C (hexanes/Et_2O); R_f = 0.26 (SiO_2, hexanes/Et_2O 100:1); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.92–7.90 (m, 1H, H-1'), 7.85 (d_{app}, J_{app} = 8.5 Hz, 1H, H-4'), 7.84–7.80 (m, 2H, H-5', H-8'), 7.71 (dd_{app}, J_{app} = 8.5, 1.8 Hz, 1H, H-3'), 7.58–7.53 (m, 2H, H-2'',6''), 7.48 (ddd_{app}, J_{app} = 8.1, 6.8, 1.5 Hz, 1H, H-7'), 7.46 (ddd_{app}, J_{app} = 8.1, 6.9, 1.4 Hz, 1H, H-6'), 7.40–7.35 (m, 2H, H-3'',5''), 7.19–7.15 (m, 1H, H-4''), 6.86 (s, 1H, H-6), 4.29 (t, J = 7.1 Hz, 2H, H-3), 3.18 (t, J = 7.4 Hz, 2H, H-1), 2.65 (pseudo-quin., $J \approx 7$ Hz, 2H, H-2); ^{13}C NMR, HSQC, HMBC (100.6 MHz, DMSO-d_6) δ (ppm) = 136.5 (C-7a), 136.4 (C-1''), 133.8 (C-8a'), 132.0 (C-4a'), 130.9 (C-2'), 129.4 (C-5), 128.7 (C-3'',5''), 128.4 (C-4'), 127.9, 127.8 (2C, C-5', C-8'), 126.5 (C-7'), 125.5 (C-6'), 125.3 (C-2'',6''), 125.1 (C-3'), 124,9 (C-4''), 123.2 (C-1'), 116.5 (C-7), 109.4 (C-6), 47.0 (C-3), 28.1 (C-2), 25.5 (C-1); IR (ATR): ν (cm^{-1}) = 3052, 2851, 1627, 1602, 1491, 1398, 1141, 818, 758, 694; ESI-HRMS calcd for $[C_{23}H_{19}N + H]^+$ 310.1596, found 310.1606.

1-(2-Bromophenyl)-3-(naphthalen-2-yl)-5,6,7,8-tetrahydroindolizine (8k). The title compound was prepared according to the general procedure from cyanopyrroline **1e** (0.190 g, 0.506 mmol, 1.0 equiv) and 1-bromo-4-chlorobutane (0.07 mL, 0.60 mmol,

1.2 equiv) using LDA (0.60 mmol, 1.2 equiv for the alkylation step, then 1.20 mmol, 2.4 equiv for the annulation step). Purification by column chromatography (SiO_2, hexanes/Et_2O 150:1→100:1) yielded **8k** (161 mg, 0.400 mmol, 79%) as a colorless solid: mp 114.5–115.5 °C (hexanes/Et_2O); R_f = 0.24 (SiO_2, hexanes/Et_2O 100:1); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.91–7.81 (m, 4H, H_{Naph}), 7.66 (dd_{app}, J_{app} = 8.0, 1.3 Hz, 1H, H-3'), 7.63 (dd_{app}, J_{app} = 8.6, 1.8 Hz, 1H, H_{Naph}), 7.52–7.43 (m, 2H, H_{Naph}), 7.39 (dd_{app}, J_{app} = 7.7, 1.8 Hz, 1H, H-6'), 7.31 (pseudo-td_{app}, $^3J_{app}$ ≈ 7.5 Hz, $^4J_{app}$ = 1.3 Hz, 1H, H-5'), 7.12 (ddd_{app}, J_{app} = 8.0, 7.3, 1.8 Hz, 1H, H-4'), 6.50 (s, 1H, H-2), 4.12 (t, J = 6.0 Hz, 2H, H-5), 2.84 (t, J = 6.4 Hz, 2H, H-8), 2.03–1.97 (m, 2H, H-6), 1.90–1.84 (m, 2H, H-7); ^{13}C NMR, HSQC, HMBC (100.6 MHz, DMSO-*d*$_6$) δ (ppm) = 137.9 (C-1'), 133.6 (Cq_{Naph}), 133.1 (C-3'), 132.2 (C-6'), 132.2 (C-3), 132.1 (Cq_{Naph}), 130.9 (Cq_{Naph}), 128.6 (C-8a), 128,0 (CH_{Naph}), 127,9 (CH_{Naph}), 127,8 (CH_{Naph}), 127,7 (C-4'), 127.4 (CH_{Naph}), 127.1 (C-5'), 126.8 (CH_{Naph}), 126.4 (CH_{Naph}), 125.8 (CH_{Naph}), 124.3 (C-2'), 120.0 (C-1), 110.7 (C-2), 45.3 (C-5), 24.1 (C-6), 23.6 (C-8), 20.9 (C-7); IR (ATR): ν (cm^{-1}) = 3053, 2944, 1628, 1600, 1326, 1025, 908, 756, 730, 639; ESI-HRMS calcd for $[C_{24}H_{20}NBr + H]^+$ 402.0857, found 402.0848.

7-(2-Bromophenyl)-5-(naphthalen-2-yl)-2,3-dihydro-1*H*-pyrrolizine (8l). The title compound was prepared according to the general procedure from cyanopyrroline **1e** (0.188 g, 0.501 mmol, 1.0 equiv) and 1-bromo-3-chloropropane (0.06 mL, 0.60 mmol, 1.2 equiv) using LDA (0.60 mmol, 1.2 equiv for the alkylation step, then 1.20 mmol, 2.4 equiv for the annulation step). Purification by column chromatography (SiO_2, hexanes/Et_2O 100:1) yielded **8l** (161 mg, 0.415 mmol, 83%) as a colorless solid: mp 159.5–160.5 °C (hexanes/Et_2O); R_f = 0.18 (SiO_2, hexanes/Et_2O 100:1); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.92–7.90 (m, 1H, H_{Naph}), 7.86–7.79 (m,

3H, H_{Naph}), 7.70 (dd_{app}, J_{app} = 8.6, 1.8 Hz, 1H, H_{Naph}), 7.66 (dd_{app}, J_{app} = 8.0, 1.3 Hz, 1H, H-3''), 7.50–7.40 (m, 3H, 2 × H_{Naph}, H-6''), 7.31 (pseudo-td_{app}, $^{3}J_{app}$ ≈ 7.5 Hz, $^{4}J_{app}$ = 1.3 Hz, 1H, H-5''), 7.10 (ddd_{app}, J_{app} = 8.0, 7.3, 1.8 Hz, 1H, H-4''), 6.81 (s, 1H, H-6), 4.33 (t, J = 7.0 Hz, 2H, H-3), 3.02 (t, J = 7.4 Hz, 2H, H-1), 2.61 (pseudo-quin., J ≈ 7 Hz, 2H, H-2); ^{13}C NMR, HSQC, HMBC (100.6 MHz, DMSO-d_6) δ (ppm) = 137.8 (C-7a), 137.5 (C-1''), 133.7 (Cq_{Naph}), 133.3 (C-3''), 131.8 (Cq_{Naph}), 131.2 (C-6''), 130.7 (Cq_{Naph}), 128.3 (2C, C-5, CH_{Naph}), 127,8 (CH_{Naph}), 127,7 (CH_{Naph}), 127,2 (2C, C-4'',5''), 126.3 (CH_{Naph}), 125.3 (CH_{Naph}), 124.9 (CH_{Naph}), 122.9 (CH_{Naph}), 122.6 (C-2''), 116.2 (C-7), 112.6 (C-6), 47.4 (C-3), 28.1 (C-2), 25.3 (C-1); IR (ATR): ν (cm^{-1}) = 3054, 2954, 1628, 1600, 1467, 1129, 1024, 906, 727, 647; ESI-HRMS calcd for $[C_{23}H_{18}NBr + H]^+$ 388.0701, found 388.0704.

1-(2-Chlorophenyl)-3-(4-fluorophenyl)-5,6,7,8-tetrahydroindolizine (8m). The title compound was prepared according to the general procedure from cyanopyrroline **1f** (0.148 g, 0.495 mmol, 1.0 equiv) and 1-bromo-4-chlorobutane (0.07 mL, 0.60 mmol, 1.2 equiv) using LDA (0.60 mmol, 1.2 equiv for the alkylation step, then 1.20 mmol, 2.4 equiv for the annulation step). Purification by column chromatography (SiO_2, hexanes/Et_2O 150:1) yielded **8m** (122 mg, 0.374 mmol, 76%) as a colorless solid: mp 112–113.5 °C (hexanes/Et_2O); R_f = 0.32 (SiO_2, hexanes/Et_2O 100:1); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.45 (dd_{app}, J_{app} = 7.9, 1.5 Hz, 1H, H-3'), 7.44–7.39 (m, 2H, H-2'',6''), 7.36 (dd_{app}, J_{app} = 7.6, 1.8 Hz, 1H, H-6'), 7.25 (pseudo-td_{app}, $^{3}J_{app}$ ≈ 7.5 Hz, $^{4}J_{app}$ = 1.5 Hz,1H, H-5'), 7.19 (pseudo-td_{app}, $^{3}J_{app}$ ≈ 7.5 Hz, $^{4}J_{app}$ = 1.8 Hz, 1H, H-4'), 7.12–7.06 (m, 2H, H-3'',5''), 6.37 (s, 1H, H-2), 3.97 (t, J = 6.0 Hz, 2H, H-5), 2.83 (t, J = 6.4 Hz, 2H, H-8), 2.01–1.94 (m, 2H, H-6), 1.88–1.81 (m, 2H, H-7); ^{13}C NMR, HSQC, HMBC (100.6 MHz, DMSO-d_6) δ (ppm) = 161.9 (d, $^{1}J_{CF}$ = 245.8 Hz, C-4''), 135.7 (C-1'),

133.5 (C-2'), 132.1 (C-6'), 131.2 (C-3), 130.5 (d, $^{3}J_{CF}$ = 8.0 Hz, C-2'',6''), 129.9 (C-3'), 129.6 (d, $^{4}J_{CF}$ = 3.1 Hz, C-1''), 128.4 (C-8a), 127,3 (C-4'), 126.5 (C-5'), 117.8 (C-1), 115.4 (d, $^{2}J_{CF}$ = 21.3 Hz, C-3'',5''), 110.1 (C-2), 45.0 (C-5), 24.0 (C-6), 23.6 (C-8), 20.9 (C-7); IR (ATR): ν (cm^{-1}) = 3058, 2944, 1594, 1524, 1488, 1222, 909, 839, 757, 732; ESI-HRMS calcd for $[C_{20}H_{17}NFCl + H]^+$ 326.1112, found 326.1119.

7-(2-Chlorophenyl)-5-(4-fluorophenyl)-2,3-dihydro-1*H*-pyrrolizine (8n). The title compound was prepared according to the general procedure from cyanopyrroline **1f** (0.148 g, 0.495 mmol, 1.0 equiv) and 1-bromo-3-chloropropane (0.06 mL, 0.60 mmol, 1.2 equiv) using LDA (0.60 mmol, 1.2 equiv for the alkylation step, then 1.20 mmol, 2.4 equiv for the annulation step). Purification by column chromatography (SiO_2, hexanes/Et_2O 150:1) yielded **8n** (114 mg, 0.366 mmol, 74%) as a light yellow amorphous solid: mp 92–95 °C (hexanes/Et_2O); R_f = 0.23 (SiO_2, hexanes/Et_2O 100:1); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) 7.50–7.40 (m, 4H, H-2',6', H-3'', H-6''), 7.25 (m, 1H, H-5''), 7.16 (ddd_{app}, J_{app} = 7.9, 7.3 1.7 Hz, 1H, H-4''), 7.11–7.05 (m, 2H, H-3',5'), 6.64 (s, 1H, H-6), 4.16 (t, J = 7.0 Hz, 2H, H-3), 3.00 (t, J = 7.3 Hz, 2H, H-1), 2.57 (pseudo-quin., $J \approx 7$ Hz, 2H, H-2); ^{13}C NMR, HSQC, HMBC (100.6 MHz, DMSO-d_6) δ (ppm) = 161.5 (d, $^{1}J_{CF}$ = 245.1 Hz, C-4'), 137.5 (C-7a), 135.4 (C-1''), 132.3 (C-2''), 130.9 (C-6''), 130.2 (C-3''), 129.7 (d, $^{4}J_{CF}$ = 3.2 Hz, C-1'), 127.8 (C-5), 127.5 (d, $^{3}J_{CF}$ = 7.8 Hz, C-2',6'), 126,9 (C-4''), 126.7 (C-5''), 115.7 (d, $^{2}J_{CF}$ = 21.5 Hz, C-3',5'), 114.3 (C-7), 111.8 (C-6), 47.0 (C-3), 28.2 (C-2), 25.6 (C-1); IR (ATR): ν (cm^{-1}) = 3061, 2976, 1593, 1525, 1480, 1221, 1157, 835, 756, 732; ESI-HRMS calcd for $[C_{19}H_{15}NFCl + H]^+$ 312.0955, found 312.0966.

3-(4-Fluorophenyl)-1-(4-methoxyphenyl)-5,6,7,8-tetrahydroindolizine (8o). The title compound was prepared according to the general procedure from cyanopyrroline **1g**

(0.147 g, 0.499 mmol, 1.0 equiv) and 1-bromo-4-chlorobutane (0.07 mL, 0.60 mmol, 1.2 equiv) using LDA (0.60 mmol, 1.2 equiv for the alkylation step, then 1.20 mmol, 2.4 equiv for the annulation step). Purification by column chromatography (SiO_2, Cy/EtOAc 20:1) yielded **8o** (131 mg, 0.408 mmol, 82%) as a colorless solid: mp 131.5–133 °C (Cy/EtOAc); R_f = 0.36 (SiO_2, Cy/EtOAc 20:1); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.42–7.36 (m, 4H, H-2',6', H-2'',6''), 7.12–7.06 (m, 2H, H-3'',5''), 6.95–6.91 (AA' part of AA'–BB' system, 2H, H-3',5'), 6.34 (s, 1H, H-2), 3.94 (t, J = 5.9 Hz, 2H, H-5), 3.83 (s, 3H, OCH_3), 3.01 (t, J = 6.4 Hz, 2H, H-8), 1.99–1.92 (m, 2H, H-6), 1.91–1.83 (m, 2H, H-7); ^{13}C NMR, HSQC, HMBC (100.6 MHz, DMSO-d_6) δ (ppm) = 162.0 (d, $^1J_{CF}$ = 246.4 Hz, C-4''), 157,4 (C-4'), 131.9 (C-3), 130.6 (d, $^3J_{CF}$ = 8.0 Hz, C-2'',6''), 129.7 (d, $^4J_{CF}$ = 3.1 Hz, C-1''), 129.5 (C-1'), 128.5 (C-2'.6'), 126.5 (C-8a), 119.9 (C-1), 115.4 (d, $^2J_{CF}$ = 21.3 Hz, C-3'',5''), 114.0 (C-3',5'), 108.0 (C-2), 55.4 (OCH_3), 45.1 (C-5), 24.1 (C-8), 23.8 (C-6), 21.2 (C-7); IR (ATR): ν (cm^{-1}) = 3071, 2937, 1573, 1503, 1244, 1178, 1158, 1033, 835, 728; ESI-HRMS calcd for $[C_{21}H_{20}NOF + H]^+$ 322.1607, found 322.1602.

5-(4-Fluorophenyl)-7-(4-methoxyphenyl)-2,3-dihydro-1*H*-pyrrolizine (8p). The title compound was prepared according to the general procedure from cyanopyrroline **1g** (0.147 g, 0.499 mmol, 1.0 equiv) and 1-bromo-3-chloropropane (0.06 mL, 0.60 mmol, 1.2 equiv) using LDA (0.60 mmol, 1.2 equiv for the alkylation step, then 1.20 mmol, 2.4 equiv for the annulation step). Purification by column chromatography (SiO_2, Cy/EtOAc 10:1) yielded **8p** (113 mg, 0.368 mmol, 74%) as a colorless solid: mp 145.5–146.5 °C (Cy/EtOAc); R_f = 0.28 (SiO_2, Cy/EtOAc 10:1); ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.48–7.41 (m, 4H, H-2',6', H-2'',6''), 7.10–7.04 (m, 2H, H-3',5'), 6.94–6.90 (AA' part of AA'–BB' system, 2H, H-3'',5''), 6.58 (s, 1H, H-2), 4.12 (t, J = 7.1 Hz,

2H, H-3), 3.83 (s, 3H, OCH_3), 3.10 (t, J = 7.3 Hz, 2H, H-8), 2.60 (pseudo-quin., $J \approx 7$ Hz, 2H, H-2); ^{13}C NMR, HSQC, HMBC (100.6 MHz, DMSO-d_6) δ (ppm) = 161.5 (d, $^1J_{CF}$ = 245.1 Hz, C-4'), 157,3 (C-4''), 135.0 (C-7a), 129.8 (d, $^4J_{CF}$ = 3.1 Hz, C-1'), 129.2 (C-1''), 128.3 (C-5), 127.5 (d, $^3J_{CF}$ = 7.8 Hz, C-2',6'), 126.4 (C-2''.6''), 116.0 (C-7), 115.7 (d, $^2J_{CF}$ = 21.5 Hz, C-3',5'), 114.2 (C-3'',5''), 108.5 (C-6), 55.5 (OCH_3), 46.6 (C-3), 28.1 (C-2), 25.3 (C-1); IR (ATR): ν (cm^{-1}) = 3061, 2954, 1601, 1505, 1290, 1245, 1178, 1157, 1034, 834; ESI-HRMS calcd for $[C_{20}H_{18}NOF + H]^+$ 308.1451, found 308.1458.

3-Methyl-1-phenyl-5,6,7,8-tetrahydroindolizine (8q). The title compound was prepared according to the general procedure from cyanopyrroline **1h** (0.095 g, 0.516 mmol, 1.0 equiv) and 1-bromo-4-chlorobutane (0.07 mL, 0.60 mmol, 1.2 equiv) using LDA (0.60 mmol, 1.2 equiv for the alkylation step, then 1.20 mmol, 2.4 equiv for the annulation step). Purification by column chromatography (SiO_2, hexanes/Et_2O 150:1) yielded **8q** (19 mg, 0.090 mmol, 17%) as a colorless oil: R_f = 0.38 (SiO_2, hexanes/Et_2O 100:1); ^{1}H NMR, COSY (600 MHz, DMSO-d_6) δ (ppm) = 7.34–7.28 (m, 4H, H-2',6', H-3',5'), 7.09–7.06 (m, 1H, H-4'), 6.00 (s, 1H, H-2), 3.76 (t, J = 6.2 Hz, 2H, H-5), 2.82 (t, J = 6.3 Hz, 2H, H-8), 2,15 (s, 3H, CH_3), 1.93–1.89 (m, 2H, H-6), 1.74–1.70 (m, 2H, H-7); ^{13}C NMR, HSQC, HMBC (150.9 MHz, DMSO-d_6) δ (ppm) = 137.1 (C-1'), 128.3 (C-3',5'), 126.4 (C-3), 126.2 (C-2',6'), 124.4 (C-8a), 124.1 (C-4'), 117.3 (C-1), 104.8 (C-2), 42.4 (C-5), 23.9 (C-8), 22.8 (C-6), 20.5 (C-7), 11.6 (CH_3); IR (ATR): ν (cm^{-1}) = 3053, 2931, 1565, 1523, 1423, 1368, 1168, 1069, 760, 698; ESI-HRMS calcd for $[C_{15}H_{17}N + H]^+$ 212.1439, found 212.1443.

1,3-Diphenyl-5,8-dihydroindolizine (14). Cyanopyrroline **1a** (0.126 g, 0.512 mmol, 1.0 equiv) was dissolved in abs. THF (10 mL) und an inert argon atmosphere at −78 °C. LDA (1.2 equiv.) was added and the resulting solution stirred for 5 minutes. The solution

was slowly added via cannula transfer to a solution of (*Z*)-1,4-dichlorobut-2-ene (0.06 mL, 0.57 mmol, 1.1 equiv) in abs. THF (10 mL) at −50 °C. The resulting solution was slowly warmed to −25 °C during 1 h, at which point LC-MS indicated full conversion of the starting material. It was again cooled to −50 °C, LDA (2.0 equiv.) was added, the resulting solution allowed to warm to ambient temperature and stirred for a further 11 h. The reaction mixture was quenched by addition of water (20 mL) and EtOAc (20 mL), the organic layer was washed with water (20 mL) then brine (20 mL) and the combined aqueous layers were extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried over sodium sulfate, concentrated in vacuo and the crude product was purified by column chromatography (SiO_2, hexanes/Et_2O 100:1) to yield **14** (28 mg, 0.103 mmol, 20%) as a light yellow oil: R_f = 0.57 (SiO_2, Cy/EtOAc 20:1); ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ (ppm) = 7.54–7.52 (m, 2H, H-2'',6''), 7.50–7.47 (m, 2H, H-2',6'), 7.45–7.41 (m, 2H, H-3'',5''), 7.39–7.34 (m, 2H, H-3',5'), 7.33–7.29 (m, 1H, H-4''), 7.19–7.15 (m, 1H, H-4'), 6.52 (s, 1H, H-2), 6.07–6.01 (m, 1H, H-7), 5.98–5.92 (m, 1H, H-6), 4.59–4.56 (m, 2H, H-5), 3.63–3.59 (m, 2H, H-8); ^{13}C NMR, HSQC, HMBC (100.6 MHz, DMSO-d_6) δ (ppm) = 136.5 (C-1'), 132.8 (C-1''), 132.2 (C-3), 128.5 (4C, C-3',5', C-3'',5''), 128.2 (C-2'',6''), 126.6 (3C, C-3',5', C-4''), 124.8 (C-4'), 123.9 (C-8a), 122.1 (C-7), 121.4 (C-6), 119.0 (C-1), 108.0 (C-2), 44.0 (C-5), 24.6 (C-8), IR (ATR): ν (cm^{-1}) = 3050, 2954, 1602, 1492, 1451, 1376, 1177, 1073, 759, 698; ESI-HRMS calcd for $[C_{20}H_{17}N + H]^+$ 272.1439, found 272.1441.

1,3-Diphenylindolizine (15). A solution of DDQ (20 mg, 0.088 mmol, 2.0) in CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of 1,3-diphenyl-5,8-dihydroindolizine (**7**, 12 mg, 0.044 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) at ambient temperature and stirring was continued for a further 15 min. The solvent was evaporated under reduced pressure and

the crude product was purified by column chromatography (SiO_2, hexanes/Et_2O 150:1) to yield **15** (7 mg, 0.026 mmol, 59%) as a light yellow oil: R_f = 0.37 (SiO_2, hexanes/Et_2O 100:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.29 (d_{app}, J_{app} = 7.3 Hz, 1H, H-5), 7.78 (dt_{app}, J_{app} = 9.1, 1.3 Hz, 1H, H-8), 7.65–7.60 (m, 4H, H_{Ph}), 7.50 (t, J_{app} = 7.8 Hz, 2H, H_{Ph}), 7.44 (t, J_{app} = 7.7 Hz, 2H, H_{Ph}), 7.37 (t, J_{app} = 7.4 Hz, 1H, H_{Ph}), 7.28–7.24 (m, 1H, H_{Ph}), 7.05 (s, 1H, H-2), 6.76 (ddd, J_{app} = 9.1, 6.3, 1.1 Hz, 1H, H-7), 6.52 (ddd, J_{app} = 7.3, 6.4, 1.3 Hz, 1H, H-6). The spectroscopic data are in accordance to the literature.[61]

Acknowledgement

The authors thank Dr. J. C. Liermann (Mainz) for NMR spectroscopy, Dr. N. Hanold (Mainz) for mass spectrometry and Dr. D. Schollmeyer (Mainz) for X-ray crystallography.

Supporting Information

^{1}H and ^{13}C NMR spectra of all new compounds, a crystal structure (ORTEP-plot), data on structure solution and refinement as well as the full crystallographic dataset (.cif-file) for compound **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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