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One-Pot Synthesis of Polysubstituted Indolizines by an Addition/Cycloaromatization Sequence

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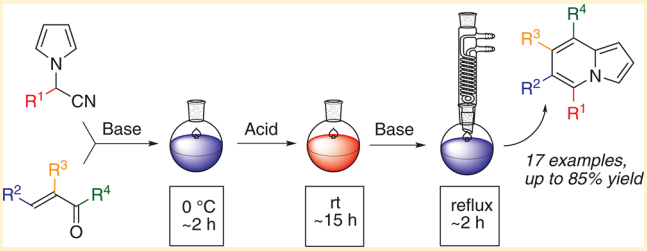
Supporting Information

ABSTRACT: Indolizines carrying various substituents in positions 5−8 were obtained from readily available 2-(1*H*-pyrrol-1-yl)nitriles and α,β-unsaturated ketones or aldehydes in a one-pot procedure. Michael addition of the deprotonated aminonitriles to the acceptors followed by acid-catalyzed electrophilic cyclization produces 5,6-dihydroindolizine-5-carbonitriles. From these stable intermediates, substituted indolizines were obtained via base-induced dehydrocyanation.



INTRODUCTION

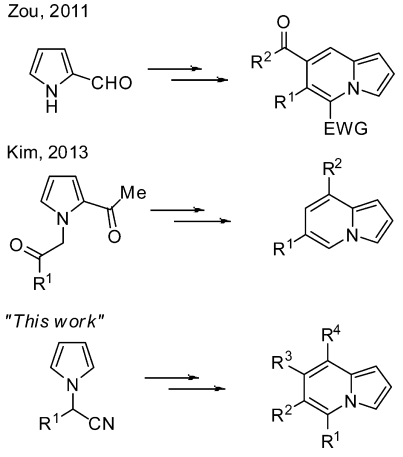
Similar to the indoles, their bioisosteric analogues, indolizines are known to possess a variety of interesting biological activities and have been classified as privileged scaffolds for the construction of GPCR ligands.[1] Other attractive bioactivities of indolizines include antitubercular,[2−4] phosphatase inhibitive,[5−7] antioxidant,[8] or anti-inflammatory.[9] Consequently, many synthetic methods have been developed for the preparation of substituted indolizines.[10,11] The majority of them start from pyridine derivatives and complete the bicyclic skeleton by construction of the pyrrole ring.[12−22] In contrast, the construction of the pyridine ring in indolizines is mostly limited to the synthesis of benzo-fused products such as pyrrolo[1,2-*a*]quinolines[23−30] and pyrrolo[2,1-*a*]isoquinolines[31−34] from 1- or 2-aryl-substituted pyrroles via the formation of C8−C8a and N−C5 bonds, respectively. As a notable exception, Kim and Lee recently reported on a cycloaromatization approach to the synthesis of 6,8-disubstituted indolizines from 2-acetylpyrroles by formation of the C6−C7 bond.[35] Likewise, annulations of the pyrrole core were achieved by formation of the C7−C8 bond in the indolizine skeleton starting from functionalized pyrrole-2-carbaldehydes, which gave indolizines devoid of a substituent in 8-position (Scheme 1).[36−41]

Here, we report a novel synthesis of indolizine with up to four substituents on the pyridine ring by means of a one-pot conjugate addition/cyclodehydration/dehydrocyanation sequence starting from 2-(1*H*-pyrrol-1-yl)nitriles and α,β-unsaturated ketones or aldehydes. In contrast to other methods,[42−47] this strategy allows the facile decoration of the pyridine unit up to persubstitution.

RESULTS AND DISCUSSION

2-(1*H*-Pyrrol-1-yl)nitriles **1a−e** can be readily prepared in a modified Clauson-Kaas procedure[48] starting from commercially available 2,5-dimethoxytetrahydrofuran and Strecker products[49−51] obtained by reaction of ammonia with the corresponding aliphatic or aromatic aldehydes (Table 1).

Scheme 1. Synthesis of Indolizines from Pyrroles



As a model reaction, we investigated the conjugate addition of deprotonated 2-(1*H*-pyrrol-1-yl)propanenitrile (**1a**) to chalcone (**2a**). The action of KHMDS (1.1 equiv) at −78 °C or KO^{t}Bu (1.1 equiv) at 0 °C on pronucleophile **1a** in THF followed by addition of electrophile **2a** afforded after 2 h a diastereomeric mixture (*syn*/*anti* 1:1) of the Michael adducts **3a** in 95% and 98% yield, respectively (Scheme 2).

In contrast, when 2-phenyl-2-(1*H*-pyrrol-1-yl)acetonitrile (**1d**) was deprotonated with different bases (e.g., KHMDS, KO^{t}Bu, LDA, NaH) and reacted with **2a** at temperatures ranging from −78 to 25 °C in DMF or THF, only low (<10% yield) or no conversion was observed. When an excess of iodomethane was added to the reaction mixture as a second electrophile, 2-phenyl-2-(1*H*-pyrrol-1-yl)propanenitrile was

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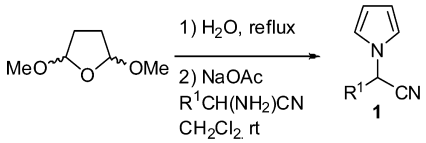
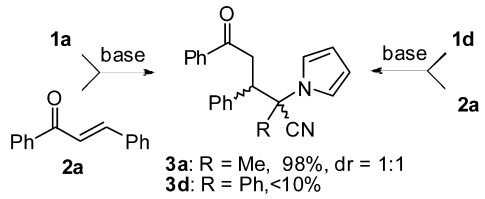
Table 1. Preparation of Pyrrolonitriles 1a−e



entry	R^1	product	yield (%)[a]
1	Me	**1a**	90[b]
2	$PhCH_2$	**1b**	76
3	^{i}Pr	**1c**	92[b]
4	Ph	**1d**	76
5	Cy	**1e**	63

[a]Isolated yield. [b]Aminonitrile hydrochloride was used.

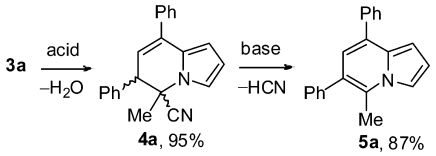
Scheme 2. Conjugate Addition of Pyrrolonitriles 1a and 1d



formed almost quantitatively (GC−MS). This proved that the deprotonation of the pronucleophile took place whereas the conjugate addition to chalcone did not. Presumably, the anion stabilizing capacity of the nitrile group and the phenyl ring in conjunction with the electron-deficient pyrrole nitrogen hampered the formation of a less stabilized ketone enolate. Thus, the conjugate addition of **1d** to **2a** in an aprotic environment should be reversible with the equilibrium being on the side of the reactants unless a better stabilization for the enolate is provided (vide infra).[52]

The product mixture **3a** was further transformed into dihydroindolizine **4a** under acidic conditions. While even the use of superstoichiometric amounts of acetic acid gave no conversion, $BF_3{\cdot}OEt_2$ (0.30 equiv) produced an appreciable yield (76%) of the cyclodehydration product **4a** (Scheme 3).

Scheme 3. Stepwise Synthesis of Indolizine 5a



This yield could be increased to 82% by using $In(OTf)_3$ (0.10 equiv) in CH_2Cl_2. However, the best result was obtained when the reaction was performed with a mixture of ethanol (5 mL/mmol pyrrolonitrile), acetic acid (7.0 equiv), and $BF_3{\cdot}OEt_2$ (3.0 equiv) in THF during 18 h at room temperature (95% yield). The base-induced dehydrocyanation of dihydroindolizine **4a** finally yielded the target indolizine **5a**. While KOH (10.0 equiv) in ethanol−water afforded **5a** in 65% yield after 3 h, DBU (10.0 equiv) in THF gave 50% yield at room temperature after 12 h. The latter figure could be improved to 87% when the mixture was heated to reflux for 2 h.

We next explored the amalgamation of all three steps to a one-pot sequence since all transformations involved can be performed in THF in high yields. This was achieved by simply adding consecutively base (KO^tBu, 1.1 equiv), acid (AcOH, 7.0 equiv/$BF_3{\cdot}OEt_2$, 3.0 equiv), and again base (DBU, 20 equiv). The overall yields obtained were comparable to those of the stepwise protocol. Table 2 summarizes the results obtained for the reaction of nitriles **1a−e** to various α,β-unsaturated carbonyl compounds (**2a−j**). It turned out that the presence of an electron-deficient α-substituent (R^3) in the electrophile required harsher conditions for the cyclodehydration. An alternative procedure (Method B, Table 2) in which the cheap AcOH/$BF_3{\cdot}OEt_2$ system was replaced by triflic acid (1.5 equiv) had to be employed in this case. While the reaction of the sterically hindered pyrrolonitrile **1c** with chalcone (**2a**) gave the indolizine **5c** in low yield (Table 2, entry 3), the reaction of pyrrolonitriles **1a**, **1b**, and **1e** with the same electrophile afforded indolizines **5a**, **5b**, and **5i** in moderate to high yield (Table 2, entries 1, 2, and 9). A similar observation was made for the reaction of **1c** with chalcone **2e** (Table 2, entries 8 and 10 compared to entry 16). 5,6,7,8-Tetrasubstituted indolizines **5f** and **5g** were synthesized from ethyl 2-benzoyl-3-phenylacrylate in 34% and 31% yield, respectively (Table 2, entries 6 and 7). The former example demonstrates that aromatic substituents R^1 can be introduced if additional enolate stabilization is provided for the product of the vinylogous addition step. Attempts to prepare the 5,6,7-trisubsubstituted indolizine **5n** from 2,3-bis(3,4-dimethoxyphenyl)acrylaldehyde in the one-pot procedure failed in the dehydrocyanation step. However, the desired product could be obtained in 39% yield by a modified two-step procedure that includes a one-pot conjugate addition/cyclodehydration sequence and dehydrocyanation of the crude dihydroindolizine **4n** with KO^tBu instead of DBU (Table 2, entry 14).

Furthermore, the one-pot sequence can be also applied to exocyclic enone systems for preparing polycyclic nitrogen heterocycles. For instance, pyrrolonitrile **1c** could be reacted with 2-(4-chlorobenzylidene)-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**2k**) and afforded tetracyclic compound **6** in 38% yield, demonstrating that no additional acceptor group in the electrophile is required to obtain persubstituted products (Scheme 4).

CONCLUSION

In summary, a new method for the synthesis of indolizines has been developed based on a one-pot sequential conjugate addition/cyclodehydration/dehydrocyanation reaction of 2-(1*H*-pyrrol-1-yl)nitriles with α,β-unsaturated carbonyl compounds. We demonstrated that this sequence can be used for the preparation of indolizines carrying up to four substituents in the pyridine portion. No expensive reagents or catalysts are required and the products were obtained in moderate to high yields. The chromatographic purification of the final products is simplified by their intense fluorescence.

EXPERIMENTAL SECTION

Compounds **2a**, 1-phenylbut-2-en-1-one (**2c**), 3-(2-chlorophenyl)-1-(4-fluorophenyl)prop-2-en-1-one (**2e**), and 3-(4-methoxyphenyl)-1-(4-fluorophenyl)prop-2-en-1-one (**2j**) were obtained from commercial suppliers. All other α,β-unsaturated aldehyde/ketones (**2b**, **2d**, **2f−2i**, and **2k**)[53,49,54−58] and α-aminonitriles[49−51] were prepared according to literature procedures.

General Procedure for the Synthesis of Pyrrolonitrile (1a−e).[48] A solution of 2,5-dimethoxytetrahydrofuran in deionized water (1.2 mL/mmol) was refluxed for 2 h. The mixture was allowed to cool before addition of CH_2Cl_2 (2 mL/mmol), the corresponding α-aminonitrile (1.0−1.2 equiv), and sodium acetate (2.4 equiv). The reaction mixture was further stirred overnight at rt. It was made

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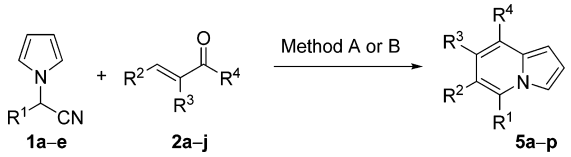
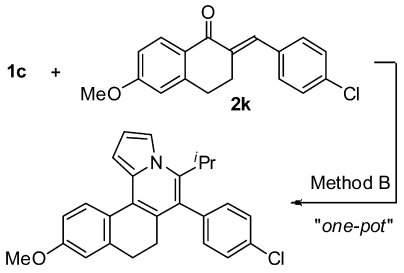
Table 2. One-Pot Synthesis of Polysubstituted Indolizines[a]



entry	R^1	R^2	R^3	R^4	product	method	yield (%)[b]
1	Me	Ph	H	Ph	**5a**	A	85
2	Bn	Ph	H	Ph	**5b**	A	54
3	^{i}Pr	Ph	H	Ph	**5c**	A	41
4	Me	Ph	H	Me	**5d**	A	31
5	Me	Me	H	Ph	**5e**	A	10
6	Me	Ph	CO_2Et	Ph	**5f**	B	31
7	Ph	Ph	CO_2Et	Ph	**5g**	B	34
8	Bn	2-Cl-C_6H_4	H	4-F-C_6H_4	**5h**	A	59
9	Cy	Ph	H	Ph	**5i**	B	69
10	Me	2-Cl-C_6H_4	H	4-F-C_6H_4	**5j**	A	67
11	Me	3,4-$(MeO)_2C_6H_3$	H	2-furyl	**5k**	A	71
12	Me	4-Cl-C_6H_4	H	^{t}Bu	**5l**	A	80
13	Me	2-thienyl	H	^{t}Bu	**5m**	A	22
14	Me	3,4-$(MeO)_2C_6H_3$	3,4-$(MeO)_2C_6H_3$	H	**5n**	A	39[c]
15	^{i}Pr	4-MeO-C_6H_4	H	4-F-C_6H_4	**5o**	A	36
16	^{i}Pr	2-Cl-C_6H_4	H	4-F-C_6H_4	**5p**	A	16

[a]Method A: (i) KO^{t}Bu, 0 °C, THF (ii) AcOH, EtOH, BF_3·OEt_2, rt (iii) DBU, reflux. Method B: (i) KO^{t}Bu, 0 °C, DMF (ii) TfOH, rt (iii) DBU, 90 °C. [b]Isolated yield. [c]The reaction was performed in two steps and KO^{t}Bu at 25 °C was used for the dehydrocyanation instead of DBU.

Scheme 4. Synthesis of a Tetracyclic Nitrogen Heterocycle



alkaline with 2 M Na_2CO_3 solution, and the crude product was extracted three times with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered, and then concentrated under reduced pressure. Further purification was either performed by filtration through a pad of silica or by vacuum distillation.

2-(1*H*-Pyrrol-1-yl)propanenitrile (1a).[59,60] Prepared according to the general procedure described above from 2-aminopropanenitrile hydrochloride[51] (5.33 g, 50.0 mmol) and 2,5-dimethoxytetrahydrofuran (5.49 g, 41.5 mmol). Distillation of the crude product yielded **1a** (4.47 g, 37.2 mmol, 90%) as a colorless liquid: bp 68−70 °C, 1 mmHg (lit.[60] bp 72−74 °C, 1.5 mmHg); R_f 0.21 (ethyl acetate/petroleum ether 1:8); IR (ATR) ν = 3104, 2993, 2946, 2248, 1488, 1277, 1100, 1053, 723, 698 cm^{-1}; ^{1}H NMR,[60] COSY (400 MHz, $CDCl_3$) δ 6.79−6.78 (AA′ part of AA′BB′ system, 2H, H2′,5′), 6.26−6.22 (BB′ part of AA′BB′ system, 2H, H3′,4′), 5.03 (q, J = 7.2 Hz, 1H, H2), 1.86 (d, J = 7.2 Hz, 3H, H3) ppm; ^{13}C NMR, HSQC, HMBC (101 MHz, $CDCl_3$) δ 119.2 (C2′,5′), 118.1 (CN), 110.3 (C3′,4′), 45.2 (C2), 21.4 (C3) ppm; ESI-MS (m/z) 121.1 (100) $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_7H_9N_2$ 121.0766, found 121.0763.

3-Phenyl-2-(1*H*-pyrrol-1-yl)propanenitrile (1b). Prepared according to the general procedure described above from 2-amino-3-phenylpropanenitrile[50] (877 mg, 6.00 mmol) and 2,5-dimethoxytetrahydrofuran (661 mg, 5.00 mmol). The crude product was further purified by column chromatography (ethyl acetate/petroleum ether 1:5) to obtain **1b** (744 mg, 3.79 mmol, 76%) as a yellow solid: mp 57−59 °C; R_f 0.24 (ethyl acetate/petroleum ether 1:5); IR (ATR) ν = 3056, 3033, 2933, 2248, 1305, 1278, 1092, 727, 700 cm^{-1}; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ 7.35−7.30 (m, 3H, H3″,5″, H4″), 7.11−7.07 (m, 2H, H2″,6″), 6.70 (AA′ part of AA′BB′ system, 2H, H2′,5′), 6.23 (BB′ part of AA′BB′ system, 2H, H3′,4′), 5.03 (t, J = 7.3 Hz, 1H, H2), 3.37 (dd, J = 13.8, 7.3 Hz, 1H, $CH_{2\text{-}a}$), 3.32 (dd, J = 13.8, 7.3 Hz, 1H, $CH_{2\text{-}b}$) ppm; ^{13}C NMR, HSQC, HMBC (101 MHz, $CDCl_3$) δ 133.9 (C1″), 129.3 (C2″,6″), 128.9 (C3″,5″), 128.0 (C4″), 119.7 (C2′,5′), 117.0 (CN), 110.1 (C3′,4′), 52.0 (C2), 42.1 (C3) ppm; ESI-MS (m/z) 393.3 (100) $[2 M + H]^+$, 235.1 (76) $[M + K]^+$, 197.1 (90) $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{13}H_{13}N_2$ 197.1079, found 197.1071.

3-Methyl-2-(1*H*-pyrrol-1-yl)butanenitrile (1c). Prepared according to the general procedure described above from 2-amino-3-methylbutanenitrile hydrochloride[51] (2.67 g, 19.8 mmol) and 2,5-dimethoxytetrahydrofuran (2.18 g, 16.5 mmol). The crude product was further purified by column chromatography (ethyl acetate/petroleum ether 1:5) to obtain **1c** (2.26 g, 15.2 mmol, 92%) as a light yellow liquid: R_f 0.34 (ethyl acetate/petroleum ether 1:5); IR (ATR) ν = 3107, 2969, 2248, 1487, 1278, 1089, 721 cm^{-1}; ^{1}H NMR, COSY (300 MHz, $CDCl_3$) δ 6.76 (AA′ part of AA′BB′ system, 2H, H2′,5′), 6.23 (BB′ part of AA′BB′ system, 2H, H3′,4′), 4.60 (d, J = 8.0 Hz, 1H, H2), 2.40−2.23 (m, 1H, H3), 1.13 (d, J = 6.8 Hz, 3H, CH_3), 0.95 (d, J = 6.8 Hz, 3H, CH_3) ppm; ^{13}C NMR, HSQC, HMBC (75 MHz, $CDCl_3$) δ 120.0 (C2′,5′), 116.7 (CN), 109.8 (C3′,4′), 57.1 (C2), 34.6 (C3), 18.7 (CH_3), 18.6 (CH_3) ppm; ESI-MS (m/z) 189.1 (100) $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_9H_{13}N_2$ 149.1079, found 149.1074.

2-Phenyl-2-(1*H*-pyrrol-1-yl)acetonitrile (1d).[61] Prepared according to the general procedure described above from 2-amino-2-phenylacetonitrile[50] (1.15 g, 8.7 mmol) and 2,5-dimethoxytetrahydrofuran (1.15 g, 8.7 mmol). The crude product was further purified by column chromatography (ethyl acetate/petroleum ether 1:5) to obtain **1d** (1.21 g, 6.7 mmol, 76%) an orange solid: mp 50−51 °C; R_f 0.29 (ethyl acetate/petroleum ether 1:5); IR (ATR) ν = 3105, 2917, 2253, 1484, 1267, 1089, 772, 695 cm^{-1}; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ 7.48−7.42 (m, 3H, H3″,5″, H4″), 7.42−7.32 (m, 2H, H2″,6″), 6.80 (AA′ part of AA′BB′ system, 2H, H2′,5′), 6.30 (BB′ part of AA′BB′ system, 2H, H3′,4′), 6.15 (s, 1H, H2) ppm; ^{13}C NMR,

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HSQC, HMBC (101 MHz, $CDCl_3$) δ 133.2 (C1″), 129.8 (C4″), 129.4 (C3″,5″), 126.8 (C2″,6″), 120.3 (C2′,5′),116.5 (CN), 110.4 (C3′,4′), 53.5 (C2) ppm; ESI-MS (m/z) 365.2 (100) $[2\ M + H]^+$, 183.1 (7) $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{11}N_2$ 183.0922, found 183.0917.

2-Cyclohexyl-2-(1*H*-pyrrol-1-yl)acetonitrile (1e). Prepared according to the general procedure described above from 2-amino-2-cyclohexylacetonitrile[49] (829 mg, 6.00 mmol) and 2,5-dimethoxytetrahydrofuran (661 mg, 5.00 mmol). The crude product was further purified by column chromatography (ethyl acetate/petroleum ether 1:10) to obtain **1e** (591 mg, 3.14 mmol, 63%) as a white solid: mp 39−40 °C; R_f 0.35 (ethyl acetate/petroleum ether 1:10); IR (ATR) ν = 2930, 2855, 2246, 1487, 1277, 1093, 720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.73 (AA′ part of AA′BB′ system, 2H, H2′,5′), 6.21 (BB′ part of AA′BB′ system, 2H, H3′,4′), 4.59 (d, J = 8.1 Hz, 1H, H2), 2.01−1.90 (m, 2H), 1.86−1.66 (m, 3H), 1.50−1.44 (m, 1H), 1.31−1.10 (m, 4H), 1.05−0.93 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.1 (C2′,5′), 116.8 (CN), 109.7 (C3′,4′), 56.4 (C2), 43.4, 29.4, 29.2, 25.8, 25.5 ppm; ESI-MS (m/z) 399.2 (100) $[2\ M + Na]^+$, 377.2 (88) $[2\ M + H]^+$, 189.1 (28) $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{12}H_{17}N_2$ 189.1392, found 189.1386.

General Procedure for the One-Pot Synthesis of Indolizines 5a−p. *Method A.* To a solution of corresponding 2-(1*H*-pyrrol-1-yl)nitrile **1a−e** in dry THF (0.1 M) at 0 °C was added a solution of KO^{t}Bu in dry THF (1.1 equiv, 1.0 M). The solution was stirred for 5 min, and a solution of corresponding α,β-unsaturated aldehyde/ketone (1.0 equiv) in dry THF (0.2 M) was added. The reaction was monitored by TLC analysis. When the conversion of the pyrrolonitrile was complete (TLC monitoring, about 2 h), the reaction was quenched with a solution of AcOH (7.0 equiv) in EtOH (1.4 M). The reaction mixture was stirred for 15−18 h at ambient temperature after $BF_3{\cdot}OEt_2$ (3.0 equiv) was added. DBU (20 equiv) was slowly added to an acidic solution (**caution, exothermic reaction**). After the mixture was heated under reflux for about 2 h (TLC monitoring), it was quenched with water (20 mL/mmol pyrrolonitrile). The product was extracted four times with EtOAc (30 mL/mmol pyrrolonitrile). The combined organic phases were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The resulting crude product was purified by column chromatography.

Method B. To a solution of corresponding 2-(1*H*-pyrrol-1-yl)nitrile **1a−e** in dry DMF (0.1 M) at 0 °C was added a solution of KO^{t}Bu (1.1 equiv) in dry DMF (0.5 M). The solution was stirred for 5 min, and a solution of the corresponding α,β-unsaturated aldehydes/ketone (1.0 equiv) in dry DMF (0.2 M) was added. When the conversion of pyrrolonitrile was complete (TLC monitoring, about 2 h), triflic acid (1.5 equiv) was added at 0 °C, and the mixture was stirred for 15−18 h at ambient temperature. DBU (20 equiv) was slowly added to an acidic solution (**caution, exothermic reaction**). After the mixture was heated to 90 °C for about 2 h (TLC monitoring), it was quenched with water (20 mL/mmol pyrrolonitrile). The product was extracted four times with EtOAc (30 mL/mmol pyrrolonitrile). The combined organic phases were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The resulting crude product was purified by column chromatography.

5-Methyl-6,8-diphenylindolizine (5a). Prepared according to method A from **1a** (120 mg, 1.00 mmol) and **2a** (208 mg, 1.00 mmol). The crude product was purified by column chromatography (petroleum ether) to obtain **5a** (242 mg, 0.85 mmol, 85%) as a yellow oil: R_f 0.14 (petroleum ether); IR (ATR) ν = 2976, 2861, 1443, 1376, 1110, 773, 759, 724, 698 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.68−7.62 (m, 2H, H_{Ph}), 7.47−7.31 (m, 9H, $8H_{Ph}$, H3), 6.89 (dd, J = 4.0, 2.8 Hz, 1H, H2), 6.68 (s, 1H, H7), 6.60 (dd, J = 4.0, 1.4 Hz, 1H, H1), 2.48 (s, 3H) ppm; ^{13}C NMR (75 MHz, CD_3OD) δ 141.5, 140.7, 133.1, 131.4, 131.0, 130.2, 129.6, 129.43, 129.37, 128.7, 128.1, 124.9, 120.8, 115.2, 112.3, 100.9, 16.4 (CH_3) ppm; ESI-MS (m/z) 284.2 (100) $[M + H]^+$, 283.2 (18) $[M]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{18}N$ 284.1439, found 284.1430.

5-Benzyl-6,8-diphenylindolizine (5b). Prepared according to method A from **1b** (196 mg, 1.00 mmol) and **2a** (208 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:5) to obtain **5b** (195 mg, 0.54 mmol, 54%) as a yellow solid: mp 180−181 °C (dec); R_f 0.57 (ethyl acetate/cyclohexane 1:5); IR (ATR) ν = 3141, 3058, 2930, 1493, 1265, 736, 699 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.78−7.74 (m, 2H), 7.53−7.49 (m, 4H), 7.48−7.43 (m, 3H), 7.43−7.36 (m, 1H), 7.30−7.25 (m, 3H), 7.22−7.15 (m, 3H), 6.82 (s, 1H, H7), 6.78 (dd, J = 4.0, 2.8 Hz, 1H, H2), 6.58 (dd, J = 4.0, 1.4 Hz, 1H, H1), 4.36 (s, 2H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 139.4, 138.3, 136.7, 130.9, 130.2, 130.1, 129.3, 128.8, 128.8, 128.6, 128.2, 128.1, 127.6, 127.4, 126.6, 124.8, 119.5, 114.4, 112.9, 99.8, 34.5 (CH_2) ppm; ESI-MS (m/z) 360.2 (100) $[M + H]^+$, 359.2 (42) $[M]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{27}H_{22}N$ 360.1752, found 360.1747.

5-Isopropyl-6,8-diphenylindolizine (5c). Prepared according to method A from **1c** (148 mg, 1.00 mmol) and **2a** (208 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:5) to obtain **5c** (127 mg, 0.41 mmol, 41%) as a white solid: mp 115−117 °C; R_f 0.80 (ethyl acetate/cyclohexane 1:5); IR (ATR) ν = 3056, 2967, 2876, 1576, 1264, 760, 734, 698 cm^{-1}; ^1H NMR, COSY (400 MHz, DMSO-d_6) δ 7.80 (dd, J = 2.8, 1.4 Hz, 1H, H3), 7.67 (m, 2H, $2H_{Ph}$), 7.51−7.36 (m, 8H, $8H_{Ph}$), 6.89 (dd, J = 4.0, 2.8 Hz, 1H, H2), 6.56 (m, 2H, H1, H7), 3.55 (sept, J = 7.0 Hz, 1H, $CH(CH_3)_2$), 1.39 (d, J = 7.0 Hz, 6H, $(CH_3)_2CH$) ppm; ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ 140.5, 138.3, 137.0 (C5), 131.6 (C8a), 129.4, 129.2 (C8), 128.7, 128.4, 128.1, 127.9, 127.2, 123.0 (C6), 120.3 (C7), 114.1 (C2), 113.8 (C3), 99.0 (C1), 29.2 ($CH(CH_3)_2$), 17.8 $(CH_3)_2CH$) ppm; ESI-MS (m/z) 312.2 (100) $[M + H]^+$, 311.2 (13) $[M^+]$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{22}N$ 312.1752, found 312.1746.

5,8-Dimethyl-6-phenylindolizine (5d). Prepared according to method A from **1a** (120 mg, 1.00 mmol) and 4-phenylbut-3-en-2-one[54] (**2b**, 146 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:5) to obtain **5d** (69 mg, 0.31 mmol, 31%) as a brown oil: R_f 0.75 (ethyl acetate/cyclohexane 1:5); IR (ATR) ν = 2928, 2857, 1493, 1394, 1280, 1025, 769, 703, 680 cm^{-1}; ^1H NMR, COSY (400 MHz, DMSO-d_6) δ 7.49−7.43 (m, 3H, H3, H3′,5′), 7.40−7.35 (m, 3H, H2′,6′, H4′), 6.85 (dd, J = 3.9, 2.7 Hz, 1H, H2), 6.56 (s, 1H, H7), 6.51 (dd, J = 3.9, 1.5 Hz, 1H, H1), 2.43 (s, 3H, 5-CH_3), 2.40 (s, 3H, 8-CH_3) ppm; ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ 139.7 (C1′), 132.8 (C8a), 129.7 (C2′,6′), 128.3 (C3′,5′), 127.6 (C5), 126.9 (C4′), 124.6 (C8), 122.5 (C6), 119.3 (C7), 113.6 (C2), 111.5 (C3), 98.3 (C1), 17.5 (5-CH_3), 15.8 (8-CH_3) ppm; ESI-MS (m/z) 222.1 (100) $[M + H]^+$, 221.1 (73) $[M]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{16}N$ 222.1283, found 222.1278.

5,6-Dimethyl-8-phenylindolizine (5e). Prepared according to method A from **1a** (120 mg, 1.00 mmol) and **2c** (146 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/petroleum ether 1:5) to obtain **5e** (21 mg, 0.10 mmol, 10%) as a red oil: R_f 0.77 (ethyl acetate/petroleum ether 1:5); IR (ATR) ν = 2924, 2853, 1444, 1377, 1279, 774, 722, 700 cm^{-1}; ^1H NMR, COSY (400 MHz, DMSO-d_6) δ 7.67−7.64 (m, 2H, H2′,6′), 7.51−7.46 (m, 2H, H3′,5′), 7.43 (dd, J = 2.7, 1.5 Hz, 1H, H3), 7.42−7.38 (m, 1H, H4′), 6.81 (dd, J = 4.0, 2.7 Hz, 1H, H2), 6.69 (s, 1H, H7), 6.49 (dd, J = 4.0, 1.5 Hz, 1H, H1), 2.49 (s, 3H, 5-CH_3), 2.31 (s, 3H, 6-CH_3) ppm; ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ 138.8 (C1′), 130.7 (C8a), 128.8 (C5), 128.72 (C8), 128.70 (C3′,5′), 128.0 (C2′,6′), 127.6 (C4′), 120.8 (C7), 115.9 (C6), 113.6 (C2), 111.0 (C3), 99.0 (C1), 17.5 (6-CH_3), 14.6 (5-CH_3) ppm; ESI-MS (m/z) 223.1 (72) $[M + H]^+$, 222.1 (100) $[M]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{16}N$ 222.1283, found 222.1277.

Ethyl 5-Methyl-6,8-diphenylindolizine-7-carboxylate (5f). Prepared according to method B from **1a** (120 mg, 1.00 mmol) and ethyl 2-benzoyl-3-phenylacrylate[55] (**2d**, 280 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:5) to obtain **5f** (109 mg, 0.31 mmol, 31%) as a light yellow oil: R_f 0.62 (ethyl acetate/cyclohexane 1:5); IR (ATR) ν = 2925, 1723, 1446, 1291, 1189,1030, 726, 697 cm^{-1}; ^1H NMR, COSY (400 MHz, DMSO-d_6) δ 7.61 (dd, J = 2.7, 1.4 Hz, 1H, H3), 7.50−7.35 (m, 8H, H_{Ph}), 7.33−7.27 (m, 2H, H_{Ph}), 6.94 (dd, J = 4.0, 2.7 Hz, 1H, H2), 6.30 (dd, J = 4.0, 1.4 Hz, 1H, H1), 3.58 (q, J = 7.1 Hz, 2H,

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OCH_2), 2.36 (s, 3H, 5-CH_3), 0.61 (t, J = 7.1 Hz, 3H, CH_3CH_2) ppm; ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ 167.4 (CO_2Et), 137.2, 136.5, 130.7 (C8a), 130.2, 130.1 (C5), 128.8, 128.4, 128.1, 128.0, 127.5, 127.3, 123.6 (C7), 120.2 (C6), 115.2 (C2), 112.9 (C3), 102.4 (C1), 60.0 (OCH_2), 16.2 (5-CH_3), 13.2 (CH_3CH_2) ppm; ESI-MS (m/z) 356.2 (100) $[M + H]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{24}H_{22}NO_2$ 356.1651, found 356.1646.

Ethyl 5,6,8-Triphenylindolizine-7-carboxylate (5g). Prepared according to method B from **1d** (182 mg, 1.00 mmol) and **2d**[55] (280 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:10) to obtain **5g** (142 mg, 0.34 mmol, 34%) as a yellow solid: mp 62−63 °C; R_f 0.36 (ethyl acetate/cyclohexane 1:10); IR (ATR) ν = 3058, 2978, 1720, 1444, 1253, 1227, 1083, 1030, 721, 695 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52−7.45 (m, 5H), 7.41−7.34 (m, 5H), 7.17−7.11 (m, 5H), 6.90 (dd, J = 2.8, 1.4 Hz, 1H, H3), 6.80 (dd, J = 4.0, 2.8 Hz, 1H, H2), 6.32 (dd, J = 4.0, 1.4 Hz, 1H, H1), 3.59 (q, J = 7.1 Hz, 2H, CH_2), 0.61 (t, J = 7.1 Hz, 3H, CH_3) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.2 (CO_2Et), 136.6, 136.2, 133.7, 133.1, 131.4, 130.5, 130.3, 129.0, 128.94, 128.93, 128.7, 128.5, 128.4, 127.4, 126.9, 124.2, 121.3, 115.1 (C2), 113.6 (C3), 102.4 (C1), 60.2 (CH_2), 13.2 (CH_3) ppm; ESI-MS (m/z) 440.2 (7) $[M + Na]^+$, 418.2 (100) $[M + H]^+$, 417.2 (2) $[M]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{29}H_{24}NO_2$ 418.1807, found 418.1800.

5-Benzyl-6-(2-chlorophenyl)-8-(4-fluorophenyl)indolizine (5h). Prepared according to method A from **1b** (196 mg, 1.00 mmol) and **2e** (261 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:10) to obtain **5h** (242 mg, 0.59 mmol, 59%) as a yellow solid: mp 71−72 °C; R_f 0.48 (ethyl acetate/cyclohexane 1:10); IR (ATR) ν = 3058, 3032, 1506, 1265, 1223, 1158, 837, 736, 696 cm^{-1}; ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ 7.80−7.74 (m, 2H, H2″,6″), 7.64−7.60 (m, 1H, H3′), 7.60−7.55 (m, 1H, H6′), 7.48−7.40 (m, 2H, H4′, H5′), 7.36−7.29 (m, 3H, H3, H3″,5″), 7.27−7.14 (m, 5H, $PhCH_2$), 6.79 (dd, J = 4.0, 2.8 Hz, 1H, H2), 6.70 (s, 1H, H7), 6.57 (dd, J = 4.0, 1.2 Hz, 1H, H1), 4.29 (d, J = 16.3 Hz, 1H, $CH_{2\text{-}a}$), 4.09 (d, J = 16.3 Hz, 1H, $CH_{2\text{-}b}$) ppm; ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ 161.9 (d, $^1J_{CF}$ = 244.9 Hz, C4‴), 137.5 (C1′), 136.1, 134.4 (d, $^4J_{CF}$ = 3.0 Hz, C1‴), 133.2 (C2′), 132.3 (C6′), 131.3 (C5), 130.9 (C8a), 130.1 (d, $^3J_{CF}$ = 8.1 Hz, C2‴,6‴), 129.8 (C4′), 129.7 (C3′), 128.73, 128.66, 127.7, 127.4 (C5′), 126.7, 122.0 (C6), 119.1 (C7), 115.6 (d, $^2J_{CF}$ = 21.4 Hz, C3‴,5‴), 114.4 (C2), 113.1 (C3), 99.9 (C1), 34.6 (CH_2) ppm; ESI-MS (m/z) 412.2 (100) $[M + H]^+$, 411.2 (64) $[M]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{27}H_{20}ClFN$ 412.1268, found 412.1265.

5-Cyclohexyl-6,8-diphenylindolizine (5i). Prepared according to method B from **1e** (188 mg, 1.00 mmol) and **2a** (208 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:5) to obtain **5i** (244 mg, 0.69 mmol, 69%) as a white solid: mp 174−175 °C; R_f 0.49 (ethyl acetate/cyclohexane 1:5); IR (ATR) ν = 2928, 2853, 1445, 1261, 1028, 760, 699 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6, 70 °C) δ 7.85 (s, 1H, H3), 7.68−7.65 (m, 2H), 7.49−7.44 (m, 4H), 7.42−7.36 (m, 4H), 6.88 (dd, J = 3.7, 3.0 Hz, 1H, H2), 6.55−6.53 (m, 2H, H1, H7), 3.20−3.14 (m, 1H), 2.33−1.59 (m, 7H), 1.34−1.12 (m, 3H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6, 70 °C) δ 140.4, 138.1, 136.3, 131.7, 129.1, 128.9, 128.3, 127.9, 127.7, 127.5, 126.8, 123.2, 120.2 (C7), 113.5 (C2), 113.3 (br, C3), 98.7 (C1), 40.6, 40.1, 26.0, 24.9 ppm; ESI-MS (m/z) 352.3 (100) $[M + H]^+$, 351.3 (53) $[M]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{26}H_{26}N$ 352.2065, found 352.2059.

6-(2-Chlorophenyl)-8-(4-fluorophenyl)-5-methylindolizine (5j). Prepared according to method A from **1a** (120 mg, 1.00 mmol) and **2e** (261 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/petroleum ether 1:10) to obtain **5j** (225 mg, 0.67 mmol, 67%) as a white solid: mp 124−125 °C; R_f 0.56 (ethyl acetate/petroleum ether 1:10); IR (ATR) ν = 3136, 3119, 3056, 2913, 1504, 1265, 1218, 1156, 837, 761, 736, 690 cm^{-1}; ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ 7.75−7.69 (m, 2H, H2″,6″), 7.61−7.58 (m, 1H, $H_{Ar'}$), 7.57 (dd, J = 2.8, 1.4 Hz, 1H, H3), 7.49−7.41 (m, 3H, $3H_{Ar'}$), 7.33−7.26 (m, 2H, H3″,5″), 6.94 (dd, J = 4.0, 2.8 Hz, 1H, H2), 6.62 (s, 1H, H7), 6.61 (d, J = 1.4 Hz, 1H, H1), 2.33 (s, 3H, CH_3) ppm; ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ 161.8 (d, $^1J_{CF}$ = 244.8 Hz, C4″), 137.7 (C1′), 134.6 (d, $^4J_{CF}$ = 3.2 Hz, C1″), 133.2 (C2′), 132.4 (C6′), 130.8 (C8a), 130.2 (C6), 130.0 (d, $^3J_{CF}$ = 8.2 Hz, C2″,6″), 129.5, 129.4, 127.8 (C8), 127.3, 120.2 (C5), 119.2 (C7), 115.6 (d, $^2J_{CF}$ = 21.4 Hz, C3″,5″), 114.6 (C2), 112.1 (C3), 99.9 (C1), 15.9 (CH_3) ppm; ESI-MS (m/z) 336.1 (100) $[M + H]^+$, 335.1 (9) $[M]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{16}ClFN$ 336.0955, found 336.0949.

6-(3,4-Dimethoxyphenyl)-8-(furan-2-yl)-5-methylindolizine (5k). Prepared according to method A from **1a** (120 mg, 1.00 mmol) and 3-(3,4-dimethoxyphenyl)-1-(furan-2-yl)prop-2-en-1-one[56] (**2f**, 258 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/petroleum ether 1:5) to obtain **5k** (237 mg, 0.71 mmol, 71%) as a light yellow solid: mp 140−142 °C (dec); R_f 0.30 (ethyl acetate/petroleum ether 1:5); IR (ATR) ν = 3055, 2934, 2834, 1505, 1257, 1240, 1025, 855, 810, 733 cm^{-1}; ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ 7.83 (d, J = 1.7 Hz, 1H, H5″), 7.55 (dd, J = 2.8, 1.4 Hz, 1H, H3), 7.18 (s, 1H, H7), 7.11 (d, J = 3.4 Hz, 1H, H3″), 7.05 (d, J = 8.3 Hz, 1H, H5′), 7.02 (d, J = 2.0 Hz, 1H, H2′), 6.99 (dd, J = 4.0, 1.4 Hz, 1H, H1), 6.96−6.93 (m, 2H, H2, H6′), 6.67 (dd, J = 3.4, 1.7 Hz, 1H, H4″), 3.81 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 2.52 (s, 3H, 5-CH_3) ppm; ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ 150.8 (C2″), 148.5 (C3′), 148.0 (C4′), 142.8 (C5″), 131.8 (C1′), 129.7 (C5), 127.5 (C8a), 122.4 (C6), 122.0 (C6′), 118.0 (C8), 116.7 (C7), 114.5 (C2), 113.6 (C2′), 112.0 (2C overlapped, C3, C4″), 111.7 (C5′), 108.1 (C3″), 100.3 (C1), 55.60 (OCH_3), 55.56 (OCH_3), 16.3 (5-CH_3) ppm; ESI-MS (m/z) 334.2 (100) $[M + H]^+$, 333.2 (15) $[M]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{21}H_{20}NO_3$ 334.1443, found 334.1440.

8-*tert*-Butyl-6-(4-chlorophenyl)-5-methylindolizine (5l). Prepared according to method A from **1a** (120 mg, 1.00 mmol) and 1-(4-chlorophenyl)-4,4-dimethylpent-1-en-3-one[49] (**2g**, 223 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:50) to obtain **5l** (238 mg, 0.80 mmol, 80%) as a white solid: mp 84−85 °C; R_f 0.41 (ethyl acetate/cyclohexane 1:50); IR (ATR) ν = 2968, 2871, 1491, 1265, 1090, 834, 732, 703 cm^{-1}; ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ 7.54−7.50 (AA′ part of AA′BB′ system, 2H, H3′,5′), 7.46−7.41 (m, 3H, H3, H2′,6′), 6.87 (dd, J = 4.1, 2.8 Hz, 1H, H2), 6.72 (dd, J = 4.1, 1.4 Hz, 1H, H1), 6.52 (s, 1H, H7), 2.42 (s, 3H, 5-CH_3), 1.45 (s, 9H, $(CH_3)_3C$) ppm; ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ 138.9 (C1′), 137.2 (C8), 131.7 (C4′), 131.6 (C2′,6′), 130.4 (C8a), 128.33 (C3′,5′), 128.29 (C5), 120.9 (C6), 115.7 (C7), 113.4 (C2), 110.9 (C3), 101.8 (C1), 34.6 ($C(CH_3)_3$), 29.6 ($(CH_3)_3C$), 16.0 (5-CH_3) ppm; ESI-MS (m/z) 298.2 (60) $[M + H]^+$, 297.2 (100) $[M]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{21}ClN$ 298.1363, found 298.1359.

8-*tert*-Butyl-5-methyl-6-(thiophen-2-yl)indolizine (5m). Prepared according to method A from **1a** (120 mg, 1.00 mmol) and 4,4-dimethyl-1-(thiophen-2-yl)pent-1-en-3-one[58] (**2h**, 149 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/petroleum ether 1:5) to obtain **5m** (58 mg, 0.22 mmol, 22%) as a yellow oil: R_f 0.73 (ethyl acetate/petroleum ether 1:5); IR (ATR) ν = 2956, 1436, 1268, 823, 760, 693 cm^{-1}; ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ 7.60 (dd, J = 5.0, 1.3 Hz, 1H, H5′), 7.45 (dd, J = 2.8, 1.3 Hz, 1H, H3), 7.16−7.12 (m, 2H, H3′, 4′), 6.87 (dd, J = 4.0, 2.8 Hz, 1H, H2), 6.72 (dd, J = 4.0, 1.3 Hz, 1H, H1), 6.61 (s, 1H, H7), 2.55 (s, 3H, 5-CH_3), 1.43 (s, 9H, $(CH_3)_3C$) ppm; ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ 141.3 (C2′), 137.1 (C8), 130.2 (C8a), 129.2 (C5), 127.4, 127.3, 126.1 (C5′), 116.2 (C7), 114.9 (C6), 113.6 (C2), 111.3 (C3), 102.1 (C1), 34.6 ($C(CH_3)_3$), 29.5 ($(CH_3)_3C$), 16.1 (5-CH_3) ppm; ESI-MS (m/z) 270.1 (100) $[M + H]^+$, 269.1 (8) $[M]^+$; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{20}NS$ 270.1317, found 270.1313.

6,7-Bis(3,4-dimethoxyphenyl)-5-methylindolizine (5n). Prepared according to modified method A. To a solution of **1a** (60 mg, 0.50 mmol) in dry THF (5 mL) at 0 °C was added a solution of KO^{t}Bu in dry THF (0.6 mL, 1.0 M). The solution was stirred for 5 min, and a solution of 2,3-bis(3,4-dimethoxyphenyl)acrylaldehyde[53] (**2i**, 104 mg, 0.50 mmol) in dry THF (2.5 mL) was added. When the

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conversion of the pyrrolonitrile was complete (TLC monitoring, about 2 h), the reaction was quenched with a solution of AcOH (0.2 mL) in EtOH (2.5 mL). The reaction mixture was stirred for 15−18 h at ambient temperature after $BF_3{\cdot}OEt_2$ (0.2 mL) was added. The reaction mixture was quenched with water (10 mL), and the dihydroindolizine was extracted three times with EtOAc (20 mL each). The combined organic phases were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. To a solution of the dihydroindolizine in dry THF (5 mL) was added a solution of KO^{t}Bu in dry THF (1.0 mL, 1.0 M), and the reaction mixture was stirred for 2 h at rt (TLC monitoring). It was quenched with water (10 mL). The product was extracted four times with EtOAc (15 mL). The combined organic phases were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The resulting crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:3) to obtain **5n** (78 mg, 0.19 mmol, 39%) as a white solid: mp 179−180 °C; R_f 0.35 (ethyl acetate/cyclohexane 1:3); IR (ATR) ν = 2998, 2933, 2834, 1509, 1248, 1135, 1024, 862, 765 cm^{-1}; ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ 7.42 (br s, 1H, H3), 7.40 (s, 1H, H7), 6.90−6.86 (m, 2H, H2, H5′), 6.80 (d, J = 8.2 Hz, 1H, H5″), 6.73 (dd, J = 8.2, 1.8 Hz, 1H, H6″), 6.67−6.64 (m, 2H, H2′, H6′), 6.53 (dd, J = 3.8, 1.1 Hz, 1H, H1), 6.48 (d, J = 1.8 Hz, 1H, H2″), 3.73 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.44 (s, 3H, OCH_3), 2.39 (s, 3H, 5-CH_3) ppm; ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ 148.0 (C3′), 147.4 (2C overlapped, C4′, C3″), 147.1 (C4″), 133.6 (C1″), 131.7 (C8a), 131.6 (C7), 130.8 (C1′), 130.6 (C5), 123.4, 122.3, 121.0 (C6″), 115.9 (C8), 115.3, 114.4 (C2), 113.3 (C2″), 111.14, 111.08, 110.5 (C3), 99.8 (C1), 55.4 (2 C overlapped), 55.3, 55.0, 16.7 (5-CH_3) ppm; ESI-MS (m/z) 436.2 (12) [M + Na]$^+$, 404.2 (100) [M + H]$^+$, 403.2 (5) [M]$^+$; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{25}H_{26}NO_4$ 404.1862, found 404.1859.

8-(4-Fluorophenyl)-5-isopropyl-6-(4-methoxyphenyl)-indolizine (5o). Prepared according to method A from **1c** (148 mg, 1.00 mmol) and **2j** (256 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/petroleum ether 1:20) to obtain **5o** (130 mg, 0.36 mmol, 36%) as a yellow solid: mp 62−64 °C; R_f 0.12 (ethyl acetate/petroleum ether 1:20); IR (ATR) ν = 2963, 2836, 1609, 1518, 1244, 1222, 1016, 832, 737, 701 cm^{-1}; ^{1}H NMR (400 MHz, CD_3CN) δ 7.73−7.66 (m, 3H, H3, H2″,6″), 7.32−7.27 (AA′ part of AA′BB′ system, 2H, H2′,6′), 7.23−7.16 (m, 2H, H3″,5″), 7.02−6.96 (BB′ part of AA′BB′ system, 2H, H3′,5′), 6.86 (dd, J = 4.0, 2.9 Hz, 1H, H2), 6.58 (s, 1H, H7), 6.54 (dd, J = 4.0, 1.4 Hz, 1H, H1), 3.83 (s, 3H, OCH_3), 3.60 (sept, J = 7.3 Hz, 1H, CH(CH$_3$)$_2$), 1.41 (d, J = 7.3 Hz, 6H, (CH_3)$_2$CH) ppm; ^{13}C NMR (75 MHz, CD_3CN) δ 163.3 (d, $^1J_{CF}$ = 244.7 Hz), 159.9, 138.6, 136.2, 136.1, 134.0, 133.2, 131.7, 131.2 (d, $^3J_{CF}$ = 8.2 Hz), 129.4, 124.1, 122.0, 116.3 (d, $^2J_{CF}$ = 21.5 Hz), 114.7, 114.6, 99.9 (C1), 56.0 (OCH_3), 30.4 (CH(CH$_3$)$_2$), 18.2 ((CH_3)$_2$CH) ppm; ESI-MS (m/z) 360.2 (100) [M + H]$^+$, 359.2 (98) [M]$^+$; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{24}H_{23}FNO$ 360.1764, found 360.1760.

6-(2-Chlorophenyl)-8-(4-fluorophenyl)-5-isopropylindolizine (5p). Prepared according to method A from **1c** (148 mg, 1.00 mmol) and **2e** (261 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/petroleum ether 1:5) to obtain **5p** (58 mg, 0.16 mmol, 16%) as a yellow oil: R_f 0.71 (ethyl acetate/petroleum ether 1:5); IR (ATR) ν = 2963, 2878, 1608, 1504, 1244, 1175, 1032, 832, 736, 701 cm^{-1}; ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ 7.81 (dd, J = 2.8, 1.2 Hz, 1H, H3), 7.72−7.66 (m, 2H, H2″,6″), 7.62−7.58 (m, 1H, $H_{Ar'}$), 7.47−7.41 (m, 3H, $H_{Ar'}$), 7.33−7.26 (m, 2H, H3″,5″), 6.91 (dd, J = 4.0, 2.8 Hz, 1H, H2), 6.56 (dd, J = 4.0, 1.2 Hz, 1H, H1), 6.43 (s, 1H, H7), 3.23 (br s, 1H, CH(CH$_3$)$_2$), 1.39 (d, J = 7.1 Hz, 3H, C$H_{3\text{-}a}$), 1.30 (br s, 3H, C$H_{3\text{-}b}$) ppm; ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ 161.8 (d, $^1J_{CF}$ = 244.8 Hz, C4″), 138.6, 137.5, 134.5 (d, $^4J_{CF}$ = 3.1 Hz, C1″), 133.1, 131.9, 131.7, 130.1 (d, $^3J_{CF}$ = 8.2 Hz, C2″,6″), 129.6, 129.4, 128.2, 127.3, 120.1, 119.5 (C7), 115.6 (d, $^2J_{CF}$ = 21.4 Hz, C3″,5″), 114.2 (C2), 113.9 (C3), 99.3 (C1), 29.9 (CH(CH$_3$)$_2$), 17.4 (CH$_3$) ppm; ESI-MS (m/z) 364.2 (100) [M + H]$^+$, 363.2 (55) [M]$^+$; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{23}H_{20}ClFN$ 364.1268, found 364.1263.

6-(4-Chlorophenyl)-5-isopropyl-10-methoxy-7,8-dihydro-benzo[*h*]pyrrolo[2,1-*a*]isoquinoline (6). Prepared according to method B from **1c** (148 mg, 1.00 mmol) and **2k**[57] (299 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:5) to obtain **6** (151 mg, 0.38 mmol, 38%) as a yellow solid: mp 158−159 °C; R_f 0.52 (ethyl acetate/petroleum ether 1:5); IR (ATR) ν = 3052, 2963, 2935, 2835, 1606, 1486, 1282, 1263, 1087, 840, 734, 699 cm^{-1}; ^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ 8.04 (d, J = 8.6 Hz, 1H, H12), 7.70 (dd, J = 2.7, 1.2 Hz, 1H, H3), 7.54−7.48 (AA′ part of AA′−BB′ system, 2H, H3′,5′), 7.31−7.26 (BB′ part of AA′−BB′ system, 2H, H2′,6′), 6.92 (dd, J = 8.6, 2.7 Hz, 1H, H11), 6.89−6.87 (m, 2H, H2, H9), 6.85 (dd, J = 4.1, 1.2 Hz, 1H, H1), 3.79 (s, 3H, OCH_3), 3.22 (br s, 1H, CH(CH$_3$)$_2$), 2.62−2.53 (m, 2H, H8), 2.13−2.04 (m, 2H, H7), 1.32 (br s, 6H, (CH_3)$_2$CH) ppm; ^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ 158.2 (C10), 139.5 (C8a), 137.7 (C4′), 136.7 (C5), 132.2 (C1′), 131.7 (C2′,6′), 129.9 (C12c), 128.6 (C3′,5′), 126.5 (C12), 126.0 (C6a), 125.5 (C12a), 121.9 (C6), 121.8 (C12b), 113.9 (C2), 113.3 (C9), 112.9 (C3), 111.5 (C11), 98.4 (C1), 55.1 (CH$_3$O), 30.1 (CH(CH$_3$)$_2$), 28.4 (C8), 26.0 (C7), 17.4 ((CH$_3$)$_2$CH) ppm; ESI-MS (m/z) 404.1 (38), 403.1 (38), 402.2 (100) [M + H]$^+$; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{26}H_{25}ClNO$ 402.1625, found 402.1621.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of compounds **1a−e**, **5a−p**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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