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Triflic Acid Mediated Cyclization of Unsymmetrical *N*-Phenethyl- and *N*-(3-Indolylethyl)succinimides: Regio- and Diastereoselective Synthesis of Substituted Pyrroloisoquinolinones and Indolizinoindolones

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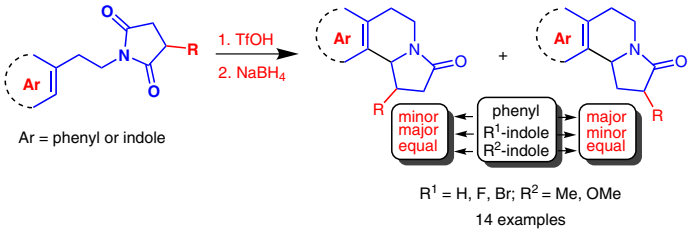

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Abstract The regio and diastereoselective synthesis of 1 or 2 alkyl-substituted pyrroloisoquinolinones and indolizinoindolones by triflic acid mediated cyclization via an electrophilic activation of unsymmetrical succinimide carbonyl groups followed by the reduction of fused cyclic *N*-acyliminium ion is reported. This strategy successfully furnished the pyrroloisoquinolinone and indolizinoindolone derivatives in regio- and diastereoselective manner. The steric factor dictates the regioselectivity in *N*-phenethyl unsymmetrical succinimides and electronic factor seems to dictate the regioselectivity in *N*-(3-indolylethyl) unsymmetrical succinimides.

Key words triflic acid, regioselectivity, diastereoselectivity, pyrroloisoquinolinones, indolizinoindolones

Pyrroloisoquinoline and indoloindolizine class of molecules, respectively, belong to the pharmacologically important tetrahydroisoquinoline and tetrahydro-β-carboline alkaloid families.[1] The alkaloids crispine A, trolline, harmicine, erysotramidine, subincanadine B, and tacamonine, for example, possesses either tetrahydroisoquinoline or tetrahydro-β-carboline skeletons (Figure 1).[2] The simple pyrroloisoquinoline[3] and indoloindolizine[4] alkaloids can be easily accessed from simple substrates. On the other hand the substituted/functionalized alkaloids, for example, erysotramidine[5] and tacamonine[6] are synthesized by either functionalizing the basic core or assembling the target molecules with regio/chemoselective manner. Several types of reactions[7] have been utilized to construct the isoquinoline units including Bischler–Napieralski reaction. Our continuous exploration of Lewis acid/Brønsted acid mediated electrophilic activation of imide carbonyl group[8] towards the synthesis of fused tetrahydroisoquinoline, tetrahydro-β-carboline derivatives, and related simple alkaloids prompted us to extend this methodology for the synthesis of more functionalized alkaloid classes by examining the stereochemical outcome of cyclization/reduction strategy with unsymmetrically substituted succinimides. The outcome of this study by subjecting the unsymmetrical succinimides under Brønsted acid mediated cyclization condition may throw a light on the possibility of using this methodology to synthesize some complex alkaloid molecules.

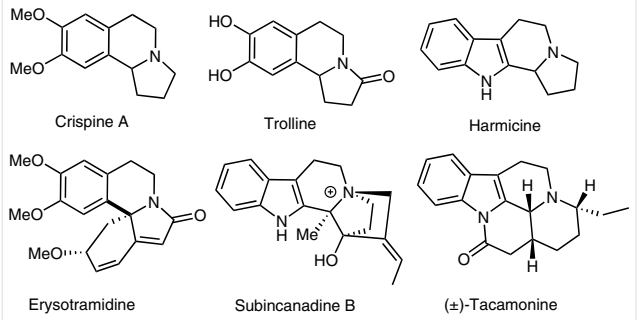


Figure 1 Simple and functionalized pyrroloisoquinoline and indoloindolizine alkaloids

Introduction of substituent at α-carbon of the succinimide unit leads to nonidentical carbonyl groups. Unsymmetrical succinimide under Brønsted acid assisted cyclization may potentially give rise to two regioisomeric mixture of fused cyclic *N*-acyliminium ions, a prochiral substrate, which on reduction using $NaBH_4$/MeOH mixture may gen-

erate a diastereomeric mixture of products due to the presence of an additional chiral center present in the imide portion (Figure 2). The α-methyl-substituted succinimide **1a** was chosen as a model substrate for this study. The succinimide **1a** was prepared in two steps from the corresponding *N*-phenethylmaleimide.[9] This *N*-phenethyl unsymmetrical succinimide was subjected to TfOH-mediated cyclization at 0 °C in dichloromethane. After the consumption of imide (monitored by TLC), the generated fused cyclic *N*-acyliminium ion was reduced with $NaBH_4$ in methanol at room temperature. The crude reaction mixture revealed the presence of two regioisomeric products in 65:35 ratio. These two regioisomers were successfully separated by column chromatography. The less sterically crowded isomer **2aa** was obtained in 58% yield while the sterically crowded regioisomer **2ab** was produced in 31% yield (Scheme 1). Interestingly, a complete diastereoselectivity was observed in this cyclization and reduction sequences. Out of two possible diastereomers (*cis* and *trans* relation between C10bH and CH_3 group) only the *trans*-diastereomer of each regioisomer was produced as evidenced from the 2D NOESY experiment. Based on the correlation observed between the hydrogen on C10b with the hydrogen on either C2 of 2-methyl isomer **2aa** or with the hydrogen on C1 of 1-methyl isomer **2ab**, the hydrogen on C10b is *trans* to either C1 or C2 substituents (*cis* to the C1 proton and C2 proton). To examine more about this regio- and diastereoselective outcome various unsymmetrical succinimides **1b–h** with different substitutions (propyl, benzyl, and benzilidine) were prepared and subjected to cyclization and reduction sequences (Table 1).

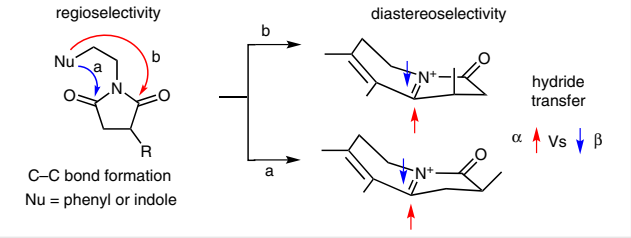
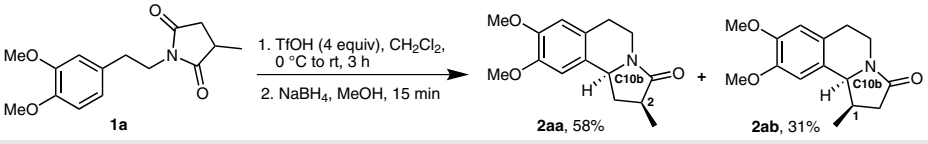


Figure 2 The regioselective cyclization and diastereoselective reduction of unsymmetrical succinimides

Formation of 2-alkyl-substituted pyrroloisoquinolinone derivatives (from imides **1a**,**b** and **1d–e**, Table 1) as major product was witnessed and that accounts for the regiochemical outcome of this cyclization reaction, which is purely dependent on the steric factor. As the steric crowd increases, the yield of 2-isomer is also increased (imide **1b**, Table 1). In certain cases with much bulkier substituents such as 3-methoxybenzyl and 3,5-dimethoxybenzyl groups, the imides exclusively produced the 2-alkyl-substituted pyrroloisoquinolinones (imides **1c**, and **1f–h**, Table 1). 2D-NMR study of these molecules also proved the existence of *trans* geometry between the hydrogen on C10b and C1/C2 substituents. These observations clearly indicate that the transfer of hydride occurred through the α-face as shown in Figure 2.

The erythrina alkaloids possess additional ring system fused at C10b and C1 position. These fused systems may potentially be derived from 1-substituted pyrroloisoquinolinone. Unfortunately, the unsymmetrical succinimides under present condition delivered both regioisomers with 1-substituted derivatives as the minor product and 2-substituted derivatives as the major component. It was assumed that the lowering of reaction temperature may alter the regioselectivity towards 1-substituted derivative. Hence, the reactions were conducted at room temperature, 0 °C, –40 °C, and –78 °C with imide **1a** (Table 2). The crude ^{1}H NMR spectra of the reaction mixture of these experiments revealed that the lowering of reaction temperature did not alter the regioisomeric ratio significantly. Surprisingly, the reaction of imide **1e** at –40 °C gave a regioisomeric ratio of 63:37 containing 37% of 1-methylpyrroloisoquinolinone; however, the same imide **1e** gave a regioisomeric ratio of 74:26 with only 26% of the 1-methyl isomer when the reaction was performed at 0 °C (Table 2). The benzyl-substituted imides **1c** and **1f** gave only 2-benzylpyrroloisoquinolinones when the reaction was performed at –40 °C. The temperature effect on the unsymmetrical succinimides further confirms that the regioselectivity and diastereoselectivity of these imides depend mainly on steric factor.

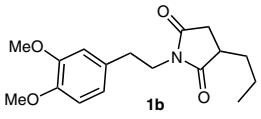
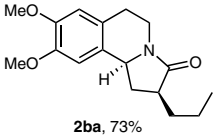
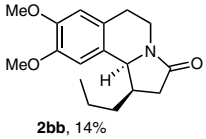
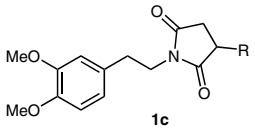
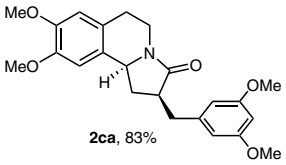
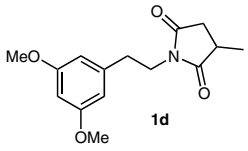
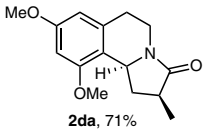
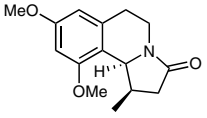
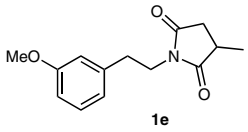
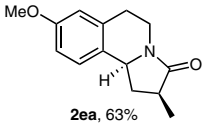
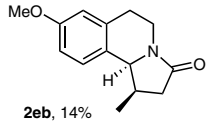
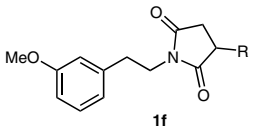
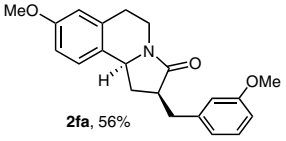
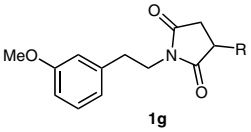
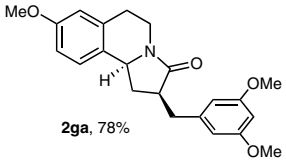
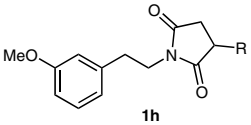
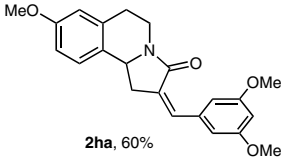
To extend this regioselective cyclization followed by diastereoselective reduction methodology to synthesize substituted β-carboline derivatives, various α-benzylated *N*-(3-indolylethyl)succinimides **3a–g** were prepared[10] and subjected to TfOH-mediated cyclization condition (Table 3). Since, all the benzyl-substituted *N*-phenethylsuccinimides delivered single regio- and diastereomers, it was speculated that the benzyl-substituted *N*-(3-indolylethyl)succinimide **3a** under standard cyclization/reduction condition would also deliver single regio- and diastereomer. In contrast to our speculation, the imide **3a** under cyclization followed by reduction condition delivered two regioisomers. Chromato-



Scheme 1 Regioselective cyclization and diastereoselective reduction of **1a**

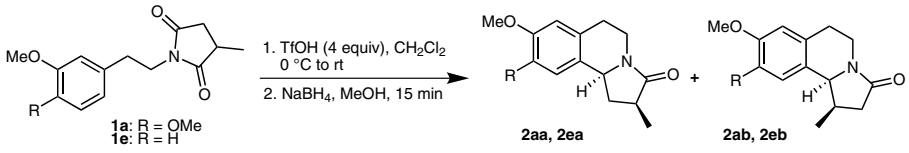
graphic separation of regioisomers by column chromatography on neutral alumina using ethyl acetate and hexane as eluents afforded the sterically hindered isomer **4ab** in 55% yield and sterically less hindered isomer **4aa** in 26% yield. The 2D NOESY analysis of the two regioisomers **4aa** and **4ab** revealed the correlation between the hydrogens of C11b and C1 of 1-benzyl isomer **4ab** and the correlation between the hydrogens of C11b and C2 of 2-benzyl isomer **4aa** confirmed the transfer of hydride occurred *trans* to the substituents face. Unsubstituted and halogen-substituted unsymmetrical succinimide derivatives of tryptamines upon treatment with TfOH produced the sterically hindered product in major quantity and steric-free product in minor quantity (from imides **3a**, **3b**, **3c**, and **3g** Table 3). But the unsymmetrical succinimide derivatives of electron-donating group-substituted tryptamines produced two regioisomeric products in nearly equal ratio (**3d**, **3e**, and **3f**, Table 3). The existence of *trans* geometry between the hydrogen on C11b and C1/C2 substituents was proven in the 2D-NMR study of these molecules and thus the diastereose-

Table 1 Effect of Substitution on Regio- and Diastereoselective Cyclization of Unsymmetrical *N*-Phenethyl Succinimides[a]

Entry	Substrate	Time (h)	Ratio	Regioisomer, yield[b]
1	 **1b**	3	81:19	 **2ba**, 73%  **2bb**, 14%
2	 **1c** R = 3,5-$(MeO)_2C_6H_3CH_2$	2	100:0	 **2ca**, 83%
3	 **1d**	2	77:23	 **2da**, 71%  **2db**, 16%
4	 **1e**	1	74:26	 **2ea**, 63%  **2eb**, 14%
5	 **1f** R = 3-$MeOC_6H_4CH_2$	1	100:0	 **2fa**, 56%
6	 **1g** R = 3,5-$(MeO)_2C_6H_3CH_2$	1	100:0	 **2ga**, 78%
7	 **1h** R = 3,5-$(MeO)_2C_6H_3CH$=	1	100:0	 **2ha**, 60%

[a] Reaction conditions: imide **1b–h** (0.5 mmol), CH_2Cl_2 (10 mL), TfOH (2 mmol), 0 °C to r.t.
[b] Yield of isolated product.

Table 2 Effect of Temperature on Regio- and Diastereoselectivity



Regioisomeric ratio **2aa**/**2ab**				Regioisomeric ratio **2ea**/**2eb**	
r.t.	0 °C	–40 °C	–78 °C	0 °C	–40 °C
67:33	65:35	64:36	62:38	74:26	63:37

lectivity during the hydride transfer step. The regioselectivity observed is quite interesting as this cyclization reduction sequence reaction may be applied to synthesize the tacamonine type of alkaloids. Single-crystal X-ray analysis of **4ba** support the relative orientation between C10b hydrogen and C2 methyl carbon is *trans* (Figure 3).[11] The reason for difference in the regioselectivity of phenyl and indole nucleophile may be explained through the possible involvement of cation–π interaction between indole nitrogen and phenyl substituents on the imide moiety during the reaction (Figure 4, a).[12]

The net positive charge on the nitrogen may be diminished when electron-donating groups are present on the indole moiety (methoxy and methyl) while this reduction in positive charge affects the magnitude of the cation–π interaction. Hence, the sterically crowded and less crowded isomers were formed in equal amounts. Such interaction is not possible with the imides **1a**–**h** and therefore sterics influence the regioselectivity.

N-Acyliminium ion cyclization is a well explored methodology for the construction of simple fused tetrahydroisoquinolines and tetrahydro-β-carbolines, but was not explored on the regioselective and diastereoselective cyclization of the unsymmetrical lactams. It is well recorded in the literature that the unsymmetrical succinimides are known to undergo regioselective partial reduction with $NaBH_4$ in methanol. It is obvious that such regioisomeric hydroxy lactams produce corresponding cyclized products in the presence of Brønsted acid. To understand the stereochemical outcome of the cyclization of the hydroxy lactam and to compare this result with direct cyclization of unsymmetrical succinimides, we carried out the cyclization of the partially reduced imide **1b** with trifluoroacetic acid (Scheme 2).[13] The less crowded isomer was formed in 31% yield and the crowded isomer was formed in 20% yield. The origin of the regioselectivity of this reaction is determined by the regioselective outcome of the partial reduction of imide carbonyl group, which is consistent with the earlier observation. The ^{1}H and 2D NOESY NMR analysis of the product reveals that the less crowded product is not a single diastereomer, rather a mixture of diastereomeres (*cis* and *trans* **2ba** + **2ba′** = 33:67) generated from *N*-acyliminium ion. The crowded isomer **2bb′** was isolated as a single diastereoisomer, which is completely *cis* (*cis*-diastereomer with respect to C10bH and *n*-propyl group). The absence of a cross peak between C10bH and C2H in 2D NOESY further confirms the nature of the product **2bb′**.

The TfOH-mediated cyclization of unsymmetrical succinimide followed by reduction of the mixture of fused cyclic *N*-acyliminium ions produced the single diastereomer of sterically crowded **2bb** and less crowded **2ba** isomers. Since the fused cyclic *N*-acyliminium ion is a rigid structure, the incoming hydride species approaches the imine bond from the less hindered side (Figure 4, b). In the case of partial reduction followed by cyclization, the generated *N*-

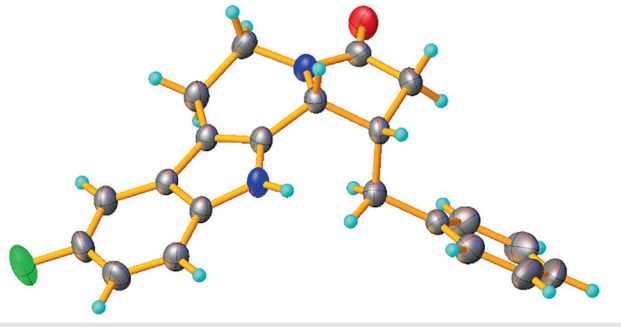


Figure 3 ORTEP diagrams for the compound **4ba** with 50% probability level

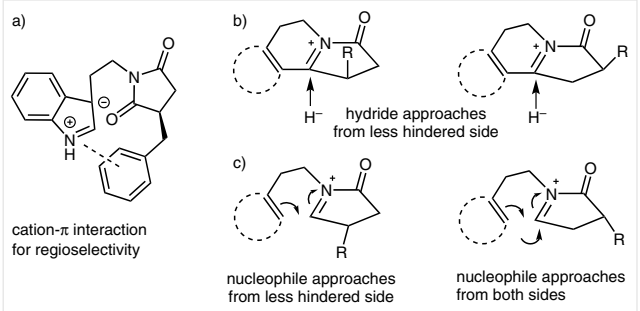
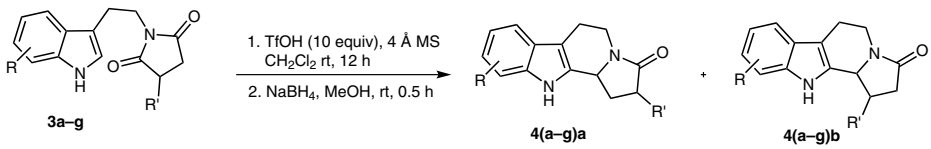
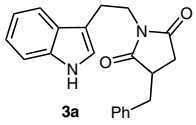
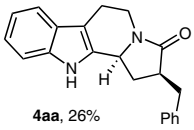
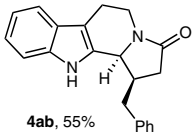
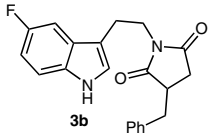
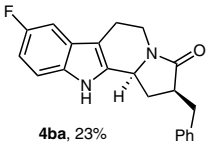
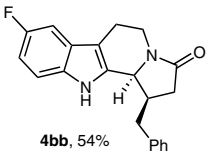
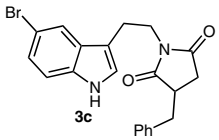
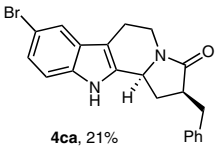
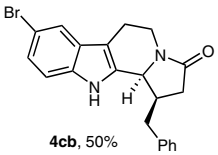
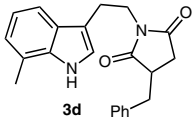
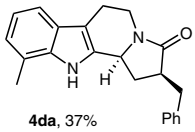
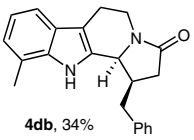
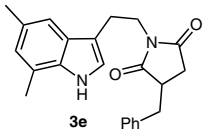
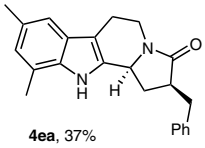
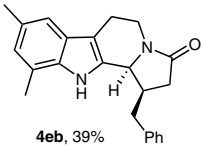
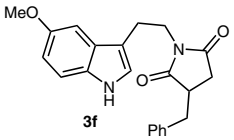
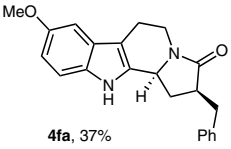
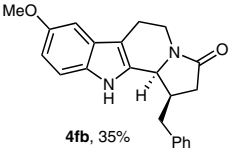
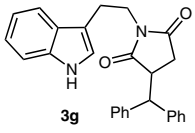
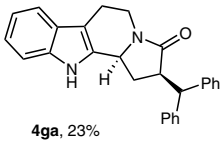
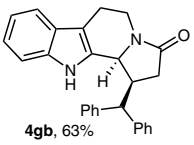


Figure 4 Schematic explanation for regio- and diastereoselectivity

Table 3 Regioselective Cyclization and Diastereoselective Reduction of *N*-(3-Indolylethyl) Unsymmetrical Succinimides[a]

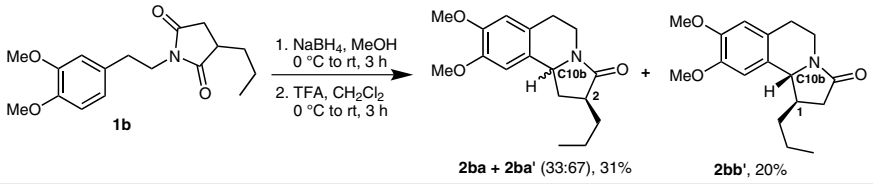


Entry	Succinimide	Regioisomer, yield[b]	
1	 **3a**	 **4aa**, 26%	 **4ab**, 55%
2	 **3b**	 **4ba**, 23%	 **4bb**, 54%
3	 **3c**	 **4ca**, 21%	 **4cb**, 50%
4	 **3d**	 **4da**, 37%	 **4db**, 34%
5	 **3e**	 **4ea**, 37%	 **4eb**, 39%
6	 **3f**	 **4fa**, 37%	 **4fb**, 35%
7	 **3g**	 **4ga**, 23%	 **4gb**, 63%

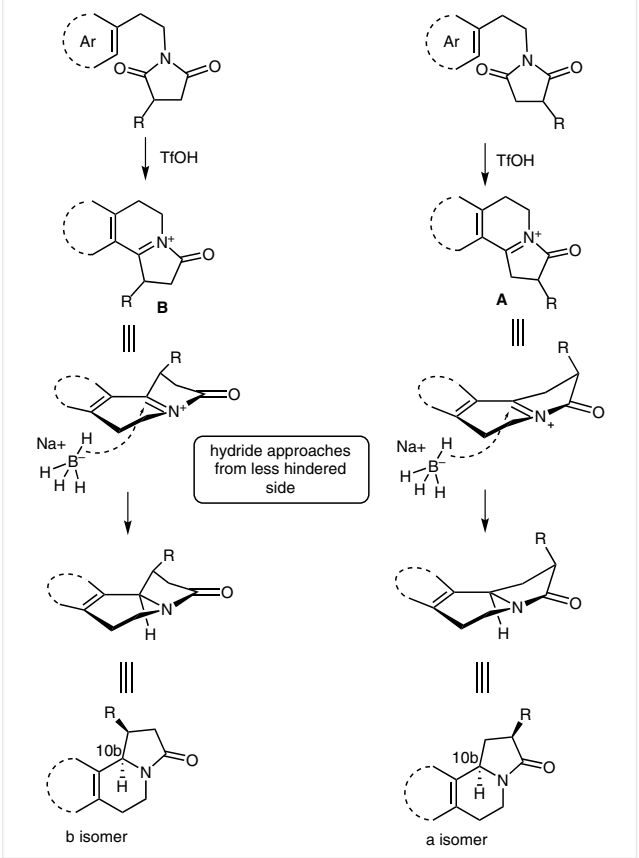
[a] Reaction conditions: imide **3a–g** (0.7 mmol), CH_2Cl_2 (10 mL), TfOH (7 mmol), 0 °C to r.t.
[b] Yield of isolated product.

acyliminium ion is linear in structure and the incoming aryl nucleophile approaches either from less hindered side to the imine double bond to produce sterically crowded product **2bb′** and a mixture of *syn*- and *anti*-addition produces the less crowded product **2ba** + **2ba′** (Figure 4, c).

Based on this observation a plausible mechanism for regioselective cyclization and distereoslective reduction is proposed (Scheme 3). The reaction may be initiated by protonation of the imide carbonyl group by TfOH followed by the intramolecular nucleophilic (aryl or heteroaryl) addition and leads to the formation of fused cyclic *N*-acylimini-



Scheme 2 *N*-Acyliminium ion cyclization of imide **1b**



Scheme 3 Mechanism for triflic acid mediated regio- and diastereoselective synthesis of tetrahydroisoquinolines and tetrahydro-β-carbolines

um ions. Due to the existence of nonidentical carbonyl groups on imides, the cyclization generated two regioisomeric *N*-acyliminium ions A and B, which upon reduction with $NaBH_4$/MeOH, produced the *trans*-isomers **a** and **b** through diastereoselective *anti*-addition (with respect to C1 or C2 substituents) of hydride source.

In conclusion, we have disclosed the regioselective cyclization of unsymmetrically substituted *N*-phenethyl- and *N*-(3-indolylethyl)succinimides by TfOH followed by diastereoselective reduction (using $NaBH_4$) to generate pharmacologically valuable pyrroloisoquinolinones and indolizinoindolones. The regio- and diastereoselectivity of the reactions are unambiguously confirmed by NMR and single crystal X-ray analysis. The switch over in the regioselectivity of the products from aryl to indole was observed for the first time. The regio- and diastereoselectivity of this cyclization reaction also compared with the *N*-acyliminium ion cyclization reaction. Further exploration of this methodology to the α-substituted *N*-phenethyl- and *N*-(3-indolylethyl)glutarimides and application to synthesize related alkaloids are in progress.

Melting points were measured with Buchi M-560 (Buchi, Switzerland) melting point apparatus. IR spectra (in cm^{-1}) were recorded on a Thermo Nicolet 6700 FT-IR spectrophotometer by using KBr thin films. HRMS data were measured by micromass Q-TOF (ESI-HRMS) and Agilent-6530 B Q-TOF (ESI-HRMS). The ^1H and ^{13}C NMR spectroscopic data were recorded on a Bruker Avance 400 spectrometer. All NMR spectra were recorded at r.t., either in $CDCl_3$ or DMSO-d_6 as solvent with TMS as an internal standard. The chemical shifts are expressed in δ (ppm) downfield from the signal of the TMS. Coupling constant (*J*-values) are given in hertz. Standard abbreviations are used to report the multiplicities of the NMR signals. X-ray crystal data were collected on an Oxford Diffraction Xcalibur diffractometer with Mo-Kα radiation (λ = 0.71073 Å). The empirical absorption correction by using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm, was applied. The structure solution and refinement were performed with SHELX-97.[14] All solvents that were used for the reactions were distilled according to standard procedures.[15] Anhyd CH_2Cl_2 was obtained by distillation over CaH_2. The substituted phenethylamines were prepared from the corresponding aldehydes by three simple synthetic steps that involved a nitroaldol condensation and a reduction of the double bond followed by nitro group reduction.[16] The reagents TfOH, phenethylamine, and 3,4-dimethoxyphenethylamine from Aldrich were used without further purification. Column chromatography was performed on Merck silica gel (100–200 mesh). The developed TLC plates (Merck 60 F 254 precoated silica plates) were visualized by using phosphomolybdic acid stain, $KMnO_4$ stain, or UV light.

For the preparation of starting unsymmetrical phenethylsuccinimides **1** and **3**, see the Supporting Information.

TfOH-Mediated Cyclization Followed by $NaBH_4$/MeOH Reduction of the Imides 1a–h; General Procedure

An oven-dried two-neck round-bottom flask bearing a septum in the side arm was cooled to r.t. under a steady stream of N_2 gas flow. The flask was charged with a stirring bar, imide **1** (0.5 mmol), and anhyd CH_2Cl_2 (15 mL), and cooled down to 0 °C (using ice). To this solution was added TfOH (0.2 mL, 2 mmol) with stirring. After 30 min, the reaction mixture was quenched with H_2O (10 mL) followed by solid

$NaHCO_3$ (1 g). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and the solvent was removed under vacuum on a rotary evaporator to dryness. The dried compound was purified by a short silica gel column chromatography using EtOAc and hexane as eluent.

2-Methyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (2aa)

Following the general procedure, the imide **1a** (138 mg, 0.5 mmol) furnished the compounds **2aa** and **2ab** as colorless semisolids after purification of the crude product mixture by silica gel column chromatography using EtOAc and hexane (30:70) as eluent.

Yield: 76 mg (58%).

IR (KBr): 2933, 2837, 1685, 1609, 1514, 1457, 1271, 1227, 1121, 1008, 858 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.61 (s, 1 H), 5.56 (s, 1 H), 4.61 (dd, *J* = 9.3, 6.6 Hz, 1 H), 4.29 (ddd, *J* = 12.7, 6.0, 2.2 Hz, 1 H), 3.86 (s, 3 H), 3.86 (s, 3 H), 3.06–2.98 (m, 1 H), 2.91–2.79 (m, 2 H), 2.70–2.60 (m, 2 H), 1.44 (td, *J* = 11.6, 9.7 Hz, 1 H), 1.22 (d, *J* = 7.04 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.44, 148.2, 148.0, 129.4, 125.6, 111.8, 107.8, 56.2, 56.0, 54.6, 37.8, 37.4, 37.2, 28.3, 15.8.

HRMS-ESI: *m*/*z* [M + Na] calcd for $C_{15}H_{19}NO_3Na^+$: 284.1263; found: 284.1261.

1-Methyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (2ab)

Yield: 40 mg (31%).

IR (KBr): 2963, 2934, 2836, 1686, 1604, 1515, 1456, 1255, 1121, 1022, 854, 796 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.61 (s, 1 H), 6.51 (s, 1 H), 4.84 (d, *J* = 4.8 Hz, 1 H), 4.38–4.33 (m, 1 H), 3.84 (s, 6 H), 2.88 (tdd, *J* = 12.1, 3.6, 1.0 Hz, 1 H), 2.83–2.73 (m, 3 H), 2.66–2.63 (m, 1 H), 2.18–2.12 (m, 1 H), 0.61 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 148.3, 147.9, 127.2, 125.5, 111.9, 108.8, 60.4, 56.2, 56.0, 40.8, 36.9, 32.8, 28.7, 15.4.

HRMS-ESI: *m*/*z* [M + Na] calcd for $C_{15}H_{19}NO_3Na^+$: 284.1263; found: 284.1268.

2-Propyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (2ba)

Following the general procedure, the imide **1b** (153 mg, 0.5 mmol) furnished the compounds **2ba** and **2bb** as colorless semisolids after purification of the crude product mixture by silica gel column chromatography using EtOAc and hexane (30:70) as eluent.

Yield: 105 mg (73%).

IR (KBr): 2958, 2932, 2870, 1686, 1610, 1514, 1456, 1362, 1255, 1114, 1012, 855, 774 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.60 (s, 1 H), 6.56 (s, 1 H), 4.61–4.57 (m, 1 H), 4.28 (ddd, *J* = 12.8, 6.0, 2.0 Hz, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.03–2.96 (m, 1 H), 2.88–2.74 (m, 2 H), 2.68–2.54 (m, 2 H), 1.95–1.89 (m, 1 H), 1.51–1.35 (m, 2 H), 1.33–1.23 (m, 2 H), 0.91 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.8, 148.0, 147.8, 129.3, 125.4, 111.6, 107.6, 56.0, 55.8, 54.6, 42.6, 36.9, 35.1, 32.8, 28.1, 20.3, 13.9.

HRMS-ESI: *m*/*z* [M + H] calcd for $C_{17}H_{24}NO_3^+$: 290.1756; found: 290.1756.

1-Propyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (2bb)

Yield: 20 mg (14%).

IR (KBr): 2949, 2849, 1692, 1612, 1512, 1447, 1362 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.62 (s, 1 H), 6.51 (s, 1 H), 4.87 (d, *J* = 5.6 Hz, 1 H), 4.35 (ddd, *J* = 12.8, 5.6, 2.0 Hz, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 2.91–2.83 (m, 1 H), 2.77 (td, *J* = 15.1, 5.0 Hz, 1 H), 2.68–2.53 (m, 3 H), 2.34 (d, *J* = 16.0 Hz, 1 H), 1.30–1.25 (m, 1 H), 1.16–1.07 (m, 1 H), 1.0–0.9 (m, 1 H), 0.85–0.81 (m, 1 H), 0.76 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 148.1, 147.8, 127.1, 125.4, 111.8, 108.8, 60.6, 56.1, 55.9, 37.9, 37.5, 36.8, 29.8, 28.7, 19.7, 14.0.

8,9-Dimethoxy-2-(3,5-dimethoxybenzyl)-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (2ca)

Following the general procedure, the imide **1c** (207 mg, 0.5 mmol) furnished the compound **2ca** as a colorless semisolid after purification of the crude product mixture by silica gel column chromatography using EtOAc and hexane (50:50) as eluent; yield: 330 mg (83%).

IR (KBr): 1997, 2934, 2836, 1690, 1594, 1514, 1430, 1362, 1256, 1116, 956 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.60 (s, 1 H), 6.49 (s, 1 H), 6.35 (d, *J* = 2.2 Hz, 1 H), 6.31 (t, *J* = 2.2 Hz, 1 H), 4.57 (dd, *J* = 8.9, 6.9 Hz, 1 H), 4.32 (ddd, *J* = 12.7, 6.0, 2.0 Hz, 1 H), 3.85 (s, 1 H), 3.83 (s, 3 H), 3.76 (s, 6 H), 3.6 (dd, *J* = 13.9, 3.7 Hz, 1 H), 3.06–2.99 (m, 1 H), 2.91–2.82 (m, 2 H), 2.70–2.60 (m, 2 H), 2.41 (dd, *J* = 13.9, 10.7 Hz, 1 H), 1.53–1.45 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9, 160.9, 148.2, 148.0, 142.3, 129.1, 125.4, 111.8, 107.8, 107.3, 106.9, 98.1, 56.1, 56.0, 55.4, 54.8, 44.9, 37.4, 37.2, 35.2, 28.3.

2-Methyl-8,10-dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (2da)

Following the general procedure, the imide **1d** (138 mg, 0.5 mmol) furnished the compounds **2da** and **2db** as colorless semisolids after purification of the crude product mixture by silica gel column chromatography using EtOAc and hexane (30:70) as eluent.

Yield: 93 mg (71%); mp 116–118 °C.

IR (KBr): 2960, 2926, 2855, 1694, 1604, 1515, 1456, 1361, 1255, 1227, 1121, 1022, 854 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.34 (d, *J* = 2.3 Hz, 1 H), 6.25 (d, *J* = 2.3 Hz, 1 H), 4.63 (dd, *J* = 9.7, 6.1 Hz, 1 H), 4.41–4.32 (m, 1 H), 3.80 (s, 3 H), 3.78 (s, 3 H), 3.05 (ddd, *J* = 12.7, 7.8, 6.1 Hz, 1 H), 2.90–2.82 (m, 2 H), 2.69–2.56 (m, 2 H), 1.29–1.21 (m, 1 H), 1.18 (d, *J* = 7.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6, 159.2, 157.7, 135.8, 118.5, 104.6, 96.9, 55.3, 55.2, 52.8, 37.6, 37.2, 36.7, 29.8, 15.6.

HRMS-ESI: *m*/*z* [M + Na] calcd for $C_{15}H_{19}NO_3Na^+$: 284.1263; found: 284.1267.

1-Methyl-8,10-dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (2db)

Yield: 21 mg (16%).

IR (KBr): 2960, 2925, 2848, 1689, 1607, 1457, 1436, 1211, 1149, 1104, 1054, 538 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.34 (d, *J* = 2.3 Hz, 1 H), 6.26 (d, *J* = 2.3 Hz, 1 H), 4.84 (d, *J* = 5.5 Hz, 1 H), 4.39–4.32 (m, 1 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.02–2.94 (m, 1 H), 2.86–2.70 (m, 3 H), 2.67–2.62 (m, 1 H), 2.06 (d, *J* = 16.2 Hz, 1 H), 0.54 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 159.3, 157.6, 137.0, 115.0, 104.6, 96.5, 58.43, 55.30, 55.26, 40.1, 36.4, 31.6, 29.9, 29.6, 15.4.

HRMS-ESI: *m*/*z* [M + Na] calcd for $C_{15}H_{19}NO_3Na^+$: 284.1263; found: 284.1260.

2-Methyl-8-methoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (2ea)

Following the general procedure, the imide **1e** (124 mg, 0.5 mmol) furnished the compounds **2ea** and **2eb** as colorless semisolids after purification of the crude product mixture by silica gel column chromatography using EtOAc and hexane (30:70) as eluent.

Yield: 73 mg (63%).

IR (KBr): 2963, 2928, 2869, 2831, 1694, 1611, 1505, 1456, 1432, 1362, 1309, 1270, 1239, 1156, 1037, 889, 806, 728, 582 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (d, *J* = 8.5 Hz, 1 H), 6.80 (dd, *J* = 8.5, 2.4 Hz, 1 H), 6.67 (d, *J* = 2.4 Hz, 1 H), 4.61 (dd, *J* = 9.3, 6.7 Hz, 1 H), 4.23 (ddd, *J* = 12.8, 6.0, 2.8 Hz, 1 H), 3.78 (s, 3 H), 3.10–3.03 (m, 1 H), 2.95–2.85 (m, 1 H), 2.83–2.71 (m, 2 H), 2.68–2.61 (m, 1 H), 1.47–1.39 (m, 1 H), 1.21 (d, *J* = 8.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.4, 158.2, 134.9, 129.8, 125.9, 113.6, 113.1, 55.3, 54.3, 37.6, 37.3, 37.0, 28.9, 15.6.

HRMS-ESI: *m*/*z* [M + Na] calcd for $C_{14}H_{17}NO_2Na^+$: 254.1157; found: 254.1155.

1-Methyl-8-methoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (2eb)

Yield: 16 mg (14%).

IR (KBr): 2963, 2928, 2866, 2834, 1697, 1612, 1434, 1362, 1243, 1311, 1243, 1034, 918, 813, 770, 586 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (d, *J* = 8.5 Hz, 1 H), 6.81 (dd, *J* = 8.5, 2.4 Hz, 1 H), 6.66 (d, *J* = 2.1 Hz, 1 H), 4.86 (d, *J* = 4.9 Hz, 1 H), 4.38–4.33 (m, 1 H), 3.79 (s, 3 H), 2.92–2.86 (m, 1 H), 2.82–2.68 (m, 4 H), 2.14 (d, *J* = 15.4 Hz, 1 H), 0.59 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 158.0, 136.0, 127.2, 125.8, 113.6, 113.2, 60.1, 55.2, 40.6, 36.5, 32.6, 29.3, 15.3.

HRMS-ESI: *m*/*z* [M + Na] calcd for $C_{14}H_{17}NO_2Na^+$: 254.1157; found: 254.1160.

8-Methoxy-2-(3-methoxybenzyl)-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (2fa)

Following the general procedure, the imide **1f** (177 mg, 0.5 mmol) furnished the compound **2fa** as a colorless semisolid after purification of the crude product mixture by silica gel column chromatography using EtOAc and hexane (50:50) as eluent.

Yield: 99 mg (56%).

IR (KBr): 1997, 2934, 2836, 1690, 1594, 1514, 1430, 1362, 1256, 1116, 1956, 829 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.17 (m, 1 H), 6.96 (d, *J* = 10.5 Hz, 1 H), 6.78–6.74 (m, 4 H), 6.66 (d, *J* = 2.3 Hz, 1 H), 4.58 (dd, *J* = 9.2, 6.8 Hz, 1 H), 4.28 (ddd, *J* = 12.8, 6.0, 2.6 Hz, 1 H), 3.78 (s, 6 H), 3.39 (dd, *J* = 13.8, 3.7 Hz, 1 H), 3.11–3.04 (m, 1 H), 2.95–2.85 (m, 2 H), 2.78–2.73 (m, 1 H), 2.65–2.59 (m, 1 H), 2.45 (dd, *J* = 13.8, 10.7 Hz, 1 H), 1.50 (td, *J* = 11.6, 9.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 159.7, 158.3, 141.4, 134.8, 129.5, 129.4, 125.9, 121.2, 114.5, 113.6, 113.1, 111.5, 55.3, 55.1, 54.5, 44.9, 37.1, 37.0, 35.0, 28.9.

HRMS-ESI: *m*/*z* [M + Na] calcd for $C_{21}H_{23}NO_3Na^+$: 360.1576; found: 360.1577.

8-Methoxy-2-(3,5-dimethoxybenzyl)-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (2ga)

Following the general procedure, the imide **1g** (192 mg, 0.5 mmol) furnished the compound **2ga** as a colorless semisolid after purification of the crude product mixture by silica gel column chromatography using EtOAc and hexane (50:50) as eluent.

Yield: 143 mg (78%).

IR (KBr): 2934, 2837, 1686, 1595, 1505, 1457, 1431, 1205, 1151, 1071, 825 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (d, *J* = 8.4 Hz, 1 H), 6.77 (dd, *J* = 8.4, 2.6 Hz, 1 H), 6.66 (d, *J* = 2.6 Hz, 1 H), 6.34 (d, *J* = 2.2 Hz, 2 H), 6.31 (t, *J* = 2.2 Hz, 1 H), 4.58 (dd, *J* = 9.2, 6.6 Hz, 1 H), 4.27 (ddd, *J* = 12.8, 6.0, 2.6 Hz, 1 H), 3.78 (s, 3 H), 3.76 (s, 6 H), 3.36 (dd, *J* = 13.8, 3.7 Hz, 1 H), 3.12–3.04 (m, 1 H), 2.95–2.83 (m, 2 H), 2.78–2.72 (m, 1 H), 2.67–2.61 (m, 1 H), 2.41 (dd, *J* = 13.8, 10.5 Hz, 1 H), 1.50 (td, *J* = 11.4, 9.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 160.9, 158.4, 142.4, 134.9, 129.7, 126.1, 113.8, 113.2, 106.9, 98.2, 55.45, 55.42, 54.6, 44.9, 37.5, 37.2, 35.2, 29.0.

HRMS-ESI: *m*/*z* [M + Na] calcd for $C_{22}H_{25}NO_4Na^+$: 390.1681; found: 390.1684.

8-Methoxy-2-(3-methoxybenzylidene)-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (2ha)

Following the general procedure, the imide **1h** (176 mg, 0.5 mmol) furnished the compound **2ha** as a colorless semisolid after purification of the crude product mixture by silica gel column chromatography using EtOAc and hexane (40:60) as eluent.

Yield: 100 mg (60%).

IR (KBr): 2998, 2963, 2849, 1686, 1649, 1589, 1505, 1455, 1427, 1264, 1064, 801, 681 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (t, *J* = 2.7 Hz, 1 H), 7.12 (d, *J* = 8.5 Hz, 1 H), 6.83 (dd, *J* = 8.5, 2.7 Hz, 1 H), 6.67 (d, *J* = 2.6 Hz, 1 H), 6.63 (d, *J* = 2.2 Hz, 1 H), 6.45 (t, *J* = 2.2 Hz, 1 H), 4.85–4.81 (m, 1 H), 4.46 (ddd, *J* = 12.9, 6.2, 2.2 Hz, 1 H), 3.82 (s, 6 H), 3.78 (s, 3 H), 3.76–3.74 (m, 1 H), 3.68 (ddd, *J* = 17.0, 7.9, 2.3 Hz, 1 H), 3.21 (ddd, *J* = 12.9, 11.4, 4.6 Hz, 1 H), 3.07–2.98 (m, 1 H), 2.94 (ddd, *J* = 17.0, 5.3, 3.2 Hz, 1 H), 2.80–2.76 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 160.8, 158.5, 137.6, 135.2, 131.7, 130.0, 129.7, 126.3, 113.7, 113.2, 107.8, 100.4, 55.4, 53.3, 54.3, 37.7, 33.7, 29.7, 28.7.

HRMS-ESI: *m*/*z* [M + Na] calcd for $C_{22}H_{23}NO_4Na^+$: 388.1525; found: 388.1594.

TfOH-Mediated Cyclization Followed by $NaBH_4$/MeOH Reduction of the Imides 3a–g; General Procedure

A 50 mL two-neck round-bottom flask was charged with imide **3** (0.7 mmol), 4Å molecular sieves (50 mg), anhyd CH_2Cl_2 (20 mL), and a stir bar. The flask was capped with a rubber septum and maintained under N_2 atmosphere. TfOH (7.6 mmol) was added and the mixture stirred at r.t. for 12 h. To this mixture were added $NaBH_4$ (3.8 mmol) and MeOH (5 mL) and stirred for 0.5 h under N_2 atmosphere. Then the mixture was quenched with aq $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with aq $NaHCO_3$, dried (Na_2SO_4), and filtered. The solvent was removed under reduced pres-

sure. The crude mixture was purified by column chromatography on neutral alumina using EtOAc/hexane (25:75) mixture as eluent to give **4aa–ga** and using EtOAc/hexane (30:70) mixture as eluent to give **4ab–gb** in pure form.

2-Benzyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (4aa)

Following the general procedure, the imide **3a** (253 mg, 0.7 mmol) furnished the compounds **4aa** and **4ab** as off-white solids.

Yield: 63 mg (26%); mp 217–218 °C.

IR (KBr): 3276, 2924, 2851, 1700, 1496, 1434, 1304, 1176 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (br s, 1 H), 7.49 (d, *J* = 7.6 Hz, 1 H), 7.32–7.26 (m, 2 H), 7.23–7.22 (m, 1 H), 7.20–7.18 (m, 1 H), 7.17–7.14 (m, 2 H), 7.12–7.10 (m, 2 H), 4.76 (dd, *J* = 9.2, 6.8 Hz, 1 H), 4.58–4.53 (m, 1 H), 3.41 (dd, *J* = 14.0, 4.0 Hz, 1 H), 3.08–3.00 (m, 1 H), 2.97–2.89 (m, 1 H), 2.83 (ddd, *J* = 9.2, 4.4, 2.0 Hz, 2 H), 2.50 (dd, *J* = 14.4, 12.0 Hz, 1 H), 2.49 (dd, *J* = 14.0, 10.8 Hz, 1 H), 1.60 (td, *J* = 11.6, 9.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.88, 139.65, 136.37, 133.14, 128.90, 128.66, 126.95, 126.47, 122.41, 120.05, 118.59, 111.10, 108.24, 52.36, 44.95, 37.71, 37.13, 33.14, 21.24.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{20}N_2O$: 317.1648; found: 317.1649.

1-Benzyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (4ab)

Yield: 132 mg (55%); mp 253–254 °C.

IR (KBr): 3266, 2924, 2853, 1668, 1492, 1437, 1311 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.19 (br s, 1 H), 7.53 (d, *J* = 7.6 Hz, 1 H), 7.30 (d, *J* = 7.6 Hz, 1 H), 7.22–7.13 (m, 5 H), 7.02–7.00 (m, 2 H), 5.11 (d, *J* = 5.6 Hz, 1 H), 4.58 (ddd, *J* = 12.4, 4.8, 1.2 Hz, 1 H), 3.08–2.95 (m, 2 H), 2.92–2.83 (m, 2 H), 2.65–2.57 (m, 2 H), 2.30 (d, *J* = 16.4 Hz, 1 H), 2.17 (dd, *J* = 14.4, 10.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.89, 139.13, 136.78, 129.91, 129.04, 128.65, 126.93, 126.45, 122.47, 119.99, 118.51, 111.25, 110.90, 58.13, 38.44, 37.79, 37.48, 35.23, 21.37.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{20}N_2O$: 317.1648; found: 317.1649.

2-Benzyl-8-fluoro-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (4ba)

Following the general procedure, the imide **3b** (230 mg, 0.7 mmol) furnished the compounds **4ba** as a viscous liquid and **4bb** as a colorless solid.

Yield: 50 mg (23%).

IR (KBr): 3171, 2976, 2896, 1670, 1427, 1309, 1183, 958 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.82 (br s, 1 H), 7.28–7.27 (m, 1 H), 7.25–7.15 (m, 4 H), 7.12 (dd, *J* = 9.6, 2.4 Hz, 2 H), 6.92 (td, *J* = 8.8, 2.4 Hz, 1 H), 4.76 (dd, *J* = 9.2, 6.8 Hz, 1 H), 4.55 (ddd, *J* = 13.2, 5.2, 2.4 Hz, 1 H), 3.42 (dd, *J* = 13.6, 4.0 Hz, 1 H), 3.08–3.01 (m, 1 H), 2.98–2.90 (m, 1 H), 2.82–2.78 (m, 2 H), 2.52 (dd, *J* = 12.0, 1.2 Hz, 1 H), 2.51 (dd, *J* = 14.0, 11.2 Hz, 1 H), 1.61 (td, *J* = 11.6, 9.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.83, 158.04 (d, *J* = 234.0 Hz, 1 C), 139.59, 135.07, 132.84, 128.92, 128.67, 127.50 (d, *J* = 10.0 Hz, 1 C), 126.51, 111.65 (d, *J* = 10.0 Hz, 1 C), 110.58 (d, *J* = 26.0 Hz, 1 C), 108.61 (d, *J* = 5.0 Hz, 1 C), 103.81 (d, *J* = 23.0 Hz, 1 C), 52.32, 44.68, 37.63, 37.12, 32.97, 21.20.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{19}FN_2O$: 335.1554; found: 335.1550.

1-Benzyl-8-fluoro-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (4bb)

Yield: 119 mg (54%); mp 273–274 °C.

IR (KBr): 3487, 2974, 2893, 1671, 1427, 1312, 1182, 960 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.76 (br s, 1 H), 7.21–7.13 (m, 5 H), 6.99 (d, *J* = 1.6 Hz, 1 H), 6.97 (d, *J* = 1.2 Hz, 1 H), 6.92 (td, *J* = 8.8, 2.4 Hz, 1 H), 5.08 (d, *J* = 6.0 Hz, 1 H), 4.58–4.54 (m, 1 H), 3.05-2.93 (m, 2 H), 2.86–2.84 (m, 2 H), 2.63 (dd, *J* = 16.4, 6.8 Hz, 1 H), 2.56 (dd, *J* = 14.4, 5.2 Hz, 1 H), 2.30 (d, *J* = 16.4 Hz, 1 H), 2.19 (dd, *J* = 14.0, 10.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.79, 158.12 (d, *J* = 234.0 Hz, 1 C), 138.99, 133.14, 131.79, 128.99, 128.70, 127.33 (d, *J* = 10.0 Hz, 1 C), 126.50, 111.81 (d, *J* = 10.0 Hz, 1 C), 111.24 (d, *J* = 4.0 Hz, 1 C), 110.68 (d, *J* = 26.0 Hz, 1 C), 103.72 (d, *J* = 23.0 Hz, 1 C), 57.96, 38.49, 37.65, 37.59, 35.34, 21.32.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{19}FN_2O$: 335.1554; found: 335.1554.

2-Benzyl-8-bromo-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (4ca)

Following the general procedure, the imide **3c** (230 mg, 0.6 mmol) furnished the compounds **4ca** and **4cb** as pale yellow solids.

Yield: 46 mg (21%); mp 212–213 °C.

IR (KBr): 3243, 2923, 2852, 1669, 1432, 1304, 1050, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.89 (br s, 1 H), 7.61 (d, *J* = 2.0 Hz, 1 H), 7.27 (d, *J* = 1.6 Hz, 1 H), 7.25–7.23 (m, 3 H), 7.19–7.15 (m, 4 H), 4.75 (dd, *J* = 9.2, 6.8 Hz, 1 H), 4.58–4.53 (m, 1 H), 3.41 (dd, *J* = 14.0, 4.0 Hz, 1 H), 3.07–2.90 (m, 2 H), 2.79 (ddd, *J* = 9.2, 5.2, 2.0 Hz, 1 H), 2.55–2.48 (m, 2 H), 1.65–1.57 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.81, 139.54, 134.98, 134.46, 128.91, 128.78, 128.67, 126.52, 125.22, 121.34, 113.28, 112.48, 108.11, 52.18, 44.86, 37.56, 37.07, 32.91, 21.10.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{19}BrN_2O$: 395.0753; found: 395.0755.

1-Benzyl-8-bromo-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (4cb)

Yield: 111 mg (50%); mp 257–258 °C.

IR (KBr): 3167, 2901, 1673, 1423, 1307, 1188, 791 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (br s, 1 H), 7.64 (s, 1 H), 7.25 (d, *J* = 5.2 Hz, 1 H), 7.20–7.15 (m, 3 H), 7.12 (d, *J* = 8.4 Hz, 1 H), 6.97 (d, *J* = 7.2 Hz, 2 H), 5.08 (d, *J* = 5.6 Hz, 1 H), 4.58–4.54 (m, 1 H), 3.06–2.90 (m, 2 H), 2.88–2.78 (m, 2 H), 2.64 (dd, *J* = 16.8, 6.8 Hz, 1 H), 2.54 (dd, *J* = 14.0, 5.6 Hz, 1 H), 2.30 (d, *J* = 16.8 Hz, 1 H), 2.20 (dd, *J* = 14.0, 10.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.83, 139.55, 135.03, 134.50, 128.93, 128.83, 128.68, 126.53, 125.23, 121.35, 113.30, 112.49, 108.14, 52.22, 44.86, 37.58, 37.09, 32.91, 21.11.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{19}BrN_2O$: 395.0753; found: 395.0749.

2-Benzyl-10-methyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (4da)

Following the general procedure, the imide **3d** (205 mg, 0.6 mmol) furnished the compounds **4da** as a viscous liquid and **4db** as a colorless solid.

Yield: 72 mg (37%).

IR (KBr): 3284, 2923, 2855, 1347, 1670, 1454, 1435 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.19 (br s, 1 H), 7.25 (d, *J* = 8.0 Hz, 1 H), 7.16–7.04 (m, 5 H), 6.97 (t, *J* = 7.6 Hz, 1 H), 6.90 (d, *J* = 7.2 Hz, 1 H), 4.68 (dd, *J* = 8.8, 6.8 Hz, 1 H), 4.67–4.42 (m, 1 H), 3.31 (dd, *J* = 14.0, 4.0 Hz, 1 H), 2.96–2.89 (m, 1 H), 2.87–2.78 (m, 1 H), 2.74–2.72 (m, 2 H), 2.49–2.43 (m, 1 H), 2.39 (s, 3 H), 2.37 (dd, *J* = 13.6, 10.8 Hz, 1 H), 1.52 (td, *J* = 11.6, 9.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.95, 139.59, 135.91, 132.90, 128.83, 128.60, 126.44, 126.41, 122.95, 120.33, 120.14, 116.17, 108.45, 52.51, 44.91, 37.75, 37.11, 33.29, 21.33, 16.81.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{22}N_2O$: 331.1804; found: 331.1804.

1-Benzyl-10-methyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (4db)

Yield: 66 mg (34%); mp 252–253 °C.

IR (KBr): 3430, 2918, 2854, 1669, 1439, 1344, 741 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.48 (br s, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 7.17–7.15 (m, 3 H), 7.06 (t, *J* = 7.6 Hz, 1 H), 7.00–6.95 (m, 3 H), 5.11 (d, *J* = 5.6 Hz, 1 H), 4.56 (ddd, *J* = 12.0, 3.6, 2.4 Hz, 1 H), 3.11–3.04 (m, 1 H), 3.00–2.87 (m, 3 H), 2.68 (dd, *J* = 16.8, 6.8 Hz, 1 H), 2.60 (dd, *J* = 14.4, 10.4 Hz, 1 H), 2.37 (s, 3 H), 2.32 (d, *J* = 16.8 Hz, 1 H), 2.28 (dd, *J* = 14.4, 9.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.92, 139.23, 136.25, 129.57, 128.91, 128.62, 126.42, 126.37, 123.17, 120.33, 120.25, 116.19, 111.66, 58.12, 38.56, 38.01, 37.84, 35.56, 21.47, 16.80.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{22}N_2O$: 331.1805; found: 331.1805.

2-Benzyl-8,10-dimethyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (4ea)

Following the general procedure, the imide **3e** (220 mg, 0.6 mmol) furnished the compounds **4ea** as a viscous liquid and **4eb** as a colorless solid.

Yield: 74 mg (37%).

IR (KBr): 3249, 2916, 2852, 1671, 1437, 1310, 1186 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.60 (br s, 1 H), 7.29–7.27 (m, 1 H), 7.25–7.24 (m, 1 H), 7.18 (td, *J* = 6.8, 1.6 Hz, 3 H), 7.13 (s, 1 H), 6.83 (s, 1 H), 4.77 (dd, *J* = 9.2, 6.8 Hz, 1 H), 4.58–4.53 (m, 1 H), 3.43 (dd, *J* = 14.0, 4.0 Hz, 1 H), 3.07–3.01 (m, 1 H), 3.00–2.90 (m, 1 H), 2.83–2.79 (m, 2 H), 2.56–2.52 (m, 1 H), 2.51–2.49 (m, 1 H), 2.42 (s, 6 H), 1.62–1.56 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.89, 139.76, 134.18, 132.98, 129.68, 128.93, 128.67, 126.80, 126.47, 124.78, 119.90, 115.99, 108.43, 52.46, 44.93, 37.76, 37.15, 33.26, 21.50, 21.35, 16.72.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{24}N_2O$: 345.1961; found: 345.1961.

1-Benzyl-8,10-dimethyl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (4eb)

Yield: 82 mg (39%); mp 236–237 °C.

IR (KBr): 3293, 2925, 2858, 1674, 1446, 1314, 1084 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.61 (br s, 1 H), 7.19–7.15 (m, 4 H), 6.98–6.96 (m, 2 H), 6.83 (s, 1 H), 5.10 (d, *J* = 5.6 Hz, 1 H), 4.57–4.52 (m, 1 H), 3.08–3.02 (m, 1 H), 2.98–2.92 (m, 1 H), 2.89–2.83 (m, 2 H), 2.66 (dd, *J* = 16.4, 7.6 Hz, 1 H), 2.60 (dd, *J* = 14.4, 6.0 Hz, 1 H), 2.43 (s, 3 H), 2.35 (s, 3 H), 2.31 (d, *J* = 16.4 Hz, 1 H), 2.24 (dd, *J* = 14.4, 10.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.90, 139.28, 134.57, 129.70, 129.58, 128.92, 128.61, 126.68, 126.34, 124.82, 120.00, 115.83, 111.11, 58.19, 38.52, 37.92, 37.85, 35.44, 21.51, 21.47, 16.75.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{24}N_2O$: 345.1961; found: 345.1961.

2-Benzyl-8-methoxy-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (4fa)

Following the general procedure, the imide **3f** (220 mg, 0.6 mmol) furnished the compounds **4fa** and **4fb** as viscous liquids.

Yield: 78 mg (37%).

IR (KBr,): 3352, 2925, 1672, 1596, 1490, 1432, 1215, 1031 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (br s, 1 H), 7.28–7.27 (m, 1 H), 7.24–7.15 (m, 5 H), 6.93 (d, *J* = 2.0 Hz, 1 H), 6.83 (dd, *J* = 8.8, 2.4 Hz, 1 H), 4.74 (dd, *J* = 8.8, 6.8 Hz, 1 H), 4.56 (ddd, *J* = 2.4, 4.4, 13.2 Hz, 1 H), 3.86 (s, 3 H), 3.41 (dd, *J* = 13.6, 4.0 Hz, 1 H), 3.08–3.01 (m, 1 H), 2.97–2.85 (m, 1 H), 2.83–2.77 (m, 2 H), 2.53–2.46 (m, 2 H), 1.60 (td, *J* = 11.6, 9.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.92, 154.48, 139.65, 134.01, 131.40, 128.90, 128.65, 127.40, 126.46, 112.27, 111.80, 108.07, 100.73, 56.07, 52.43, 44.92, 37.72, 37.12, 33.11, 21.29.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{22}N_2O_2$: 347.1754; found: 347.1754.

1-Benzyl-8-methoxy-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (4fb)

Yield: 74 mg (35%).

IR (KBr): 3318, 2921, 1670, 1632, 1432, 1216, 1032 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.19 (br s, 1 H), 7.22–7.13 (m, 4 H), 7.01–6.99 (m, 2 H), 6.98 (d, *J* = 2.4 Hz, 1 H), 6.84 (dd, *J* = 8.8, 2.4 Hz, 1 H), 5.08 (d, *J* = 6.0 Hz, 1 H), 4.59–4.54 (m, 1 H), 3.87 (s, 3 H), 3.03–2.95 (m, 2 H), 2.88–2.84 (m, 2 H), 2.63–2.57 (m, 2 H), 2.30 (d, *J* = 16.4 Hz, 1 H), 2.16 (dd, *J* = 11.2, 2.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.92, 154.41, 139.14, 131.81, 130.77, 129.04, 128.63, 127.31, 126.41, 112.35, 111.97, 110.59, 100.59, 58.17, 56.07, 38.45, 37.78, 37.43, 35.17, 21.43.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{22}N_2O_2$: 347.1755, found: 347.1755.

2-Benzhydryl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (4ga)

Following the general procedure, the imide **3g** (250 mg, 0.6 mmol) furnished the compounds **4ga** and **4gb** as pale brown solids.

Yield: 55 mg (23%); mp 254–255 °C.

IR (KBr): 3425, 2925, 2830, 1629, 1355 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 (br s, 1 H), 7.44 (d, *J* = 7.6 Hz, 1 H), 7.31 (d, *J* = 4.0 Hz, 4 H), 7.25–7.10 (m, 4 H), 7.07–7.04 (m, 4 H), 6.95–6.94 (m, 1 H), 4.83–4.79 (m, 1 H), 4.59 (d, *J* = 6.0 Hz, 1 H), 4.50 (dd, *J* = 13.2, 4.8 Hz, 1 H), 3.60–3.53 (m, 1 H), 3.00 (td, *J* = 11.2, 4.8 Hz, 1 H), 2.77–2.68 (m, 2 H), 2.65–2.59 (m, 1 H), 1.78–1.70 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.24, 143.46, 142.02, 136.29, 132.90, 128.88, 128.54, 128.35 (2 C merging), 127.03, 126.61, 126.49, 122.31, 119.97, 118.51, 111.01, 108.47, 52.18, 51.16, 46.83, 37.78, 30.92, 21.13.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{24}N_2O$: 393.1961; found: 393.1962.

1-Benzhydryl-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (4gb)

Yield: 151 mg (63%); mp 230–231 °C.

IR (KBr): 3419, 2924, 2830, 1705, 1628, 1592, 1490, 1350 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 7.6 Hz, 1 H), 7.38–7.37 (m, 2 H), 7.33 (t, *J* = 7.6 Hz, 2 H), 7.25–7.22 (m, 3 H), 7.17–7.12 (m, 3 H), 7.11–7.05 (m, 2 H), 6.97–6.95 (m, 2 H), 5.24 (d, *J* = 6.8 Hz, 1 H), 4.50–4.45 (m, 1 H), 4.00 (d, *J* = 11.6 Hz, 1 H), 3.76–3.67 (m, 1 H), 3.00–2.90 (m, 2 H), 2.75–2.71 (m, 1 H), 2.32 (dd, *J* = 17.2, 8.0 Hz, 1 H), 2.19 (dd, *J* = 17.2, 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.53, 143.23, 143.14, 136.39, 129.81, 129.62, 129.07, 127.80, 127.55, 127.45, 127.01, 126.54, 122.38, 119.71, 118.30, 111.99, 111.09, 58.52, 52.46, 41.00, 39.20, 37.17, 20.84.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{24}N_2O^+$: 393.1961; found: 393.1966.

2-Propyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (2ba + 2ba′)

The partial reduction was conducted with imide **1b** (153 mg, 0.5 mmol) using $NaBH_4$/MeOH and the mixture of hydroxy lactams were subjected to *N*-acyliminium ion cyclization using TFA;[13] yield: 45 mg (31%); colorless viscous liquid.

IR (KBr): 2962, 2856, 1683, 1606, 1514, 1459, 1368 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.57–6.65 (m, 1 H), 6.54–6.53 (m, 1 H), 4.68 (t, *J* = 7.6 Hz, 0.65 H), 4.99–4.55 (m, 0.31 H), 4.28–4.23 (m, 1 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.00–2.93 (m, 1 H), 2.85–2.77 (m, 1.4 H), 2.63–2.59 (m, 1 H), 2.48–2.46 (m, 1 H), 2.23–2.31 (m, 0.66 H), 2.02–1.97 (m, 0.36 H), 1.68–1.78 (m, 0.7 H), 1.48–1.23 (m, 3 H), 0.94–0.87 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.7, 174.8, 148.10, 148.0, 147.8, 129.6, 129.3, 125.6, 125.4, 111.7, 107.7, 56.0, 55.9, 55.1, 54.6, 42.8, 42.7, 37.2, 37.0, 35.2, 33.4, 33.1, 32.9, 28.2, 28.0, 20.7, 20.4, 14.0, 13.98.

1-Propyl-8,9-dimethoxy-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (2bb′)

Yield: 29 mg (20%); colorless viscous liquid.

IR (KBr): 2928, 2862, 1686, 1607, 1514, 1456, 1367 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.70 (s, 1 H), 6.60 (s, 1 H), 4.36 (d, *J* = 6.4 Hz, 1 H), 4.26–4.21 (m, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.00–2.97 (m, 1 H), 2.90–2.82 (m, 1 H), 2.63–2.54 (m, 2 H), 2.26–2.19 (m, 2 H), 1.98–1.91 (m, 1 H), 1.63–1.59 (m, 1 H), 1.51–1.47 (m, 1 H), 1.42–1.34 (m, 1 H), 0.98 (t, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 148.0, 147.9, 129.4, 126.5, 111.9, 107.9, 62.2, 56.1, 56.00, 41.0, 38.1, 37.7, 37.4, 28.4, 20.9, 14.2.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588639.

References

(1) (a) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2012**, *75*, 311. (b) *The Alkaloids: Chemistry and Biology*; Vol. 1–70; Elsevier: Amsterdam, **1983**. (c) *Dictionary of Alkaloids*, 2nd ed.; Buckingham, J.; Baggaley, K. H.; Roberts, A. D.; Szabó, L. F., Eds.; CRC Press: Boca Raton, **2010**.

(2) (a) Ernst, E.; Pittler, M. H. *J. Urol.* **1998**, *159*, 433. (b) Vas, A.; Gulyas, B. *Med. Res. Rev.* **2005**, *25*, 737. (c) Takayama, H.; Ishikawa, H.; Kurihara, M.; Kitajima, M.; Aimi, N.; Ponglux, D.; Koyama, F.; Matsumoto, K.; Moriyama, T.; Yamamoto, L. T.; Watanabe, K.; Murayama, T.; Horie, S. J. *J. Med. Chem.* **2002**, *45*, 1949.

(3) (a) Xu, X. M.; Zhao, L.; Zhu, J.; Wang, M. X. *Angew. Chem. Int. Ed.* **2016**, *55*, 3799. (b) Prabhu, G.; Agarwal, S.; Sharma, V.; Madurkar, S. M.; Munshi, P.; Singh, S.; Sen, S. *Eur. J. Med. Chem.* **2015**, *95*, 41. (c) Ledovskaya, M. S.; Molchanov, A. P.; Boitsov, V. M.; Kostikov, R. R.; Stepakov, A. V. *Tetrahedron* **2015**, *71*, 1952. (d) De Carne-Carnavalet, B.; Krieger, J. P.; Folleas, B.; Brayer, J. L.; Demoute, J. P.; Meyer, C.; Cossy, J. *Eur. J. Org. Chem.* **2015**, 1273. (e) Kalaitzakis, D.; Montagnon, T.; Antonatou, E.; Bardaji, N.; Vassilikogiannakis, G. *Chem. Eur. J.* **2013**, *19*, 10119. (f) De Carne-Carnavalet, B.; Meyer, C.; Cossy, J.; Folleas, B.; Brayer, J. L.; Demoute, J. P. *J. Org. Chem.* **2013**, *78*, 5794. (g) Perard-Viret, J.; Souquet, F.; Manisse, M. L.; Royer, J. *Tetrahedron Lett.* **2010**, *51*, 96. (h) Camarero, C.; Gonzalez-Temprano, I.; Gomez-SanJuan, A.; Arrasate, S.; Lete, E.; Sotomayor, N. *Tetrahedron* **2009**, *65*, 5787. (i) Gonzalez-Temprano, I.; Osante, I.; Lete, E.; Sotomayor, N. *J. Org. Chem.* **2004**, *69*, 3875. (j) Simpkins, N. S.; Gill, C. D. *Org. Lett.* **2003**, *5*, 535. (k) Allin, S. M.; Gaskell, S. N.; Towler, J. M. R.; Page, P. C. B.; Saha, B.; McKenzie, M. J.; Martin, W. P. *J. Org. Chem.* **2007**, *72*, 8972. (l) Jebali, K.; Planchat, A.; Amri, H.; Allainmat, M. M.; Lebreton, J. *Synthesis* **2016**, *48*, 1502.

(4) (a) Hua, D. H.; Bharathi, S. N.; Panangadan, J. A. K.; Tsujimoto, A. *J. Org. Chem.* **1991**, *56*, 6998. (b) Deiters, A.; Chen, K.; Eary, C. T.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 4541. (c) Martin, S. F.; Benage, B.; Hunter, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 5925. (d) Birman, V. B.; Rawal, V. H. *Tetrahedron Lett.* **1998**, *39*, 7219. (e) Mizuno, T.; Oonishi, Y.; Takimoto, M.; Sato, Y. *Eur. J. Org. Chem.* **2011**, 2606. (f) Gomez, A. G.; Domínguez, G.; Castells, J. P. *Tetrahedron Lett.* **2005**, *46*, 7267. (g) Poissonnet, G.; Bettiol, M. H. T.; Dodd, R. H. *J. Org. Chem.* **1996**, *61*, 2273. (h) Sydorenko, N.; Zificsak, C. A.; Gerasyuto, A. I.; Hsung, R. P. *Org. Biomol. Chem.*

2005, *3*, 2140. (i) Paulvannan, K.; Hale, R.; Mesis, R.; Chen, T. *Tetrahedron Lett.* **2002**, *43*, 203. (j) Karpov, A. S.; Oeser, T.; Müller, T. J. J. *Chem. Commun.* **2004**, 1502.

(5) (a) Homme, C. L.; Ménard, M. A.; Canesi, S. *J. Org. Chem.* **2014**, *79*, 8481. (b) Tietze, L. F.; Tölle, N.; Kratzert, D.; Stalke, D. *Org. Lett.* **2009**, *11*, 5230. (c) Paladino, M.; Zaifman, J.; Ciufolini, M. A. *Org. Lett.* **2015**, *17*, 3422. (d) Lee, H.; Cassidy, M. P.; Rashatasakhon, P.; Padwa, A. *Org. Lett.* **2003**, *5*, 5067. (e) Onoda, T.; Takikawa, Y.; Fujimoto, T.; Yasui, Y.; Suzuki, K.; Matsumoto, T. *Synlett* **2009**, 1041. (f) Blake, A. J.; Gill, C.; Greenhalgh, D. A.; Simpkins, N. A.; Zhang, F. *Synthesis* **2005**, 3287.

(6) (a) Takasu, K.; Nishida, N.; Tomimura, A.; Ihara, M. *J. Org. Chem.* **2005**, *70*, 3957. (b) Ho, T. L.; Lin, Q. X. *Tetrahedron* **2008**, *64*, 10401. (c) Deiters, A.; Pettersson, M.; Martin, S. F. *J. Org. Chem.* **2006**, *71*, 6547. (d) Danieli, B.; Lesma, G.; Macecchini, S.; Passarella, D.; Alessandra, S. *Tetrahedron: Asymmetry* **1999**, *20*, 4057.

(7) (a) Bischler, A.; Napieralski, B. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 1903. (b) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341. (c) Heravi, M. M.; Khaghaninejad, S.; Nazari, N. *Adv. Heterocycl. Chem.* **2014**, *112*, 183.

(8) (a) Selvakumar, J.; Makriyannis, A.; Ramanathan, C. R. *Org. Biomol. Chem.* **2010**, *8*, 4056. (b) Selvakumar, J.; Ramanathan, C. R. *Org. Biomol. Chem.* **2011**, *9*, 7643. (c) Mangalaraj, S.; Ramanathan, C. R. *RSC Adv.* **2012**, *2*, 12665. (d) Selvakumar, J.; Sreenivasa Rao, R.; Srinivasapriyan, V.; Marutheeswaran, S.; Ramanathan, C. R. *Eur. J. Org. Chem.* **2015**, 2175. (e) Mangalaraj, S.; Selvakumar, J.; Ramanathan, C. R. *J. Chem. Sci.* **2015**, *127*, 811.

(9) Wang, J.; Liu, H.; Fan, Y.; Yang, Y.; Jiang, Z.; Tan, C.-H. *Chem. Eur. J.* **2010**, *16*, 12534.

(10) (a) Hu, C.; Qin, H.; Cui, Y.; Jia, Y. *Tetrahedron* **2009**, *65*, 9075. (b) Eriks, J. C.; Van der Goot, H.; Sterk, G. J.; Timmerman, H. *J. Med. Chem.* **1992**, *35*, 3239. (c) Dutta, S.; Kim, S-K.; Patel, D. B.; Kim, T-J.; Chang, Y. *Polyhedron* **2007**, *26*, 3799. (d) Yanagi, T.; Kikuchi, K.; Takeuchi, H.; Ishikawa, T.; Nishimura, T.; Kamijo, T.; Yamamoto, I. *Chem. Pharm. Bull.* **2001**, *49*, 340.

(11) CCDC 1476191 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(12) Kennedy, C. R.; Lin, S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2016**, *55*, 2.

(13) (a) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. (b) Blake, A. J.; Gill, C.; Greenhalgh, D. A.; Simpkins, N. S.; Zhang, F. *Synthesis* **2005**, 3287.

(14) Sheldrick, G. M. *SHELX-97, Programs for the Solution and Refinement of Crystal Structures*; University of Göttingen: Germany, **1997**.

(15) Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 6th ed.; Elsevier: Oxford, **2009**.

(16) (a) Merchant, J. R.; Mountwala, A. J. *J. Org. Chem.* **1958**, *23*, 1774. (b) Sinhababu, A. K.; Borchardt, R. T. *Tetrahedron Lett.* **1983**, *24*, 227. (c) Trost, B. M.; Yeh, V. S. C.; Ito, H.; Bremeyer, N. *Org. Lett.* **2002**, *4*, 2621. (d) Pei, Z.; Li, L.; Geldern, T. W.; Longenecker, K.; Pireh, D.; Stewart, K. D.; Backes, B. J.; Lai, C.; Lubben, T. H.; Ballaron, S. J.; Beno, D. W. A.; Grote, A. J.; Sham, H. L.; Trevillyan, J. M. *J. Med. Chem.* **2007**, *50*, 1983.