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Synthesis of Aminoindolizidines through the Chemoselective and Diastereoselective Catalytic Hydrogenation of Indolizines

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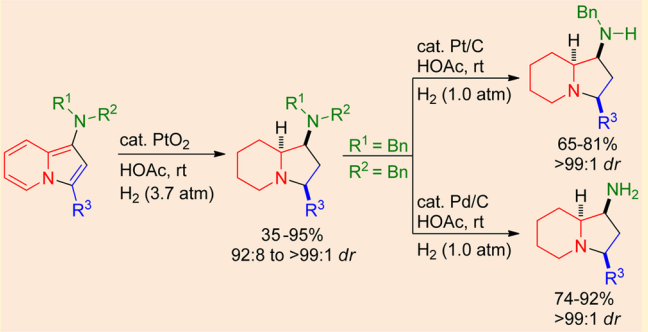
Supporting Information

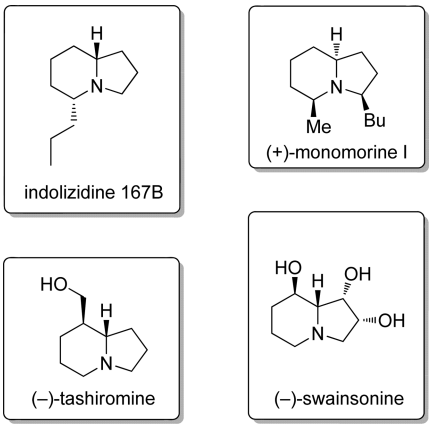
ABSTRACT: Indolizidines are bioactive heterocyclic compounds of great potential normally prepared following multistep routes. However, to the best of our knowledge, the synthesis of 1-aminoindolizidines has never been reported. Herein, 1-(dialkylamino)-3-substituted indolizidines have been straightforwardly synthesized using an atom-economic protocol that involves a copper-catalyzed three-component synthesis of indolizines followed by heterogeneous catalytic hydrogenation. The latter was found to be chemoselective using platinum(IV) oxide as the catalyst at 3.7 atm, providing the aminoindolizidines in modest-to-high yields (35−95%) and high diastereoselectivity (92:8 to >99:1). It has been experimentally demonstrated that the hydrogenation occurs through the intermediate 5,6,7,8-tetrahydroindolizine, which contains a pyrrole moiety. Moreover, the diastereomerically pure 1-(dibenzylamino)-3-substituted indolizidines could be further transformed into the corresponding monobenzylated or fully debenzylated aminoindolizidines by selective hydrogenolysis catalyzed by Pt/C or Pd/C, respectively, under ambient conditions.



INTRODUCTION

There is a general upsurge of interest in developing new strategies to effectively obtain saturated N-heterocycles from readily accessible starting materials. This demand is supported by the potential development of new pharmaceuticals related to this type of heterocycles and their natural abundance.[1] Among them, indolizidine alkaloids are widespread in nature and have attracted a great deal of attention because of their structural diversity and varied biological activity (Chart 1).[2] For instance, indolizidine 167B was first found as a minor constituent in the skin secretions of a batrachian of the genus *Dendrobates*,[3] whereas (+)-monomorine I was isolated from both Pharaoh's ant *Monomorium pharaonis* and from bufonid toads of the *Melanopbryniscus* genus.[4] (−)-Tashiromine was first isolated from the stems of *Maackia Tashiroi* (Leguminosae),[5a] a bush from subtropical Asia, and later on from leaves and seeds of the *Poecilanthe*[5b] genus and from Ethiopian *Crotalaria* species.[5c] Swainsonine was first identified in the Australian legume *Swainsona canescens*[6a] and, subsequently, as the toxin in *Astragalus* and *Oxytropis* species that cause locoism in livestock.[6b] In contrast, the significance of swainsonine in the treatment of cancer and in immunology has been reported.[6c] Indolizidines have also played an important role in the synthesis of other natural products.[7]

Chart 1. Structure of Some Naturally Occurring Indolizidines



Different synthetic strategies have been developed to construct the indolizidine skeleton according to the substitution pattern pursued,[8] including (a) by using pyrroles as building blocks,[9] (b) from α-amino acids via stereocontrolled rhodium-catalyzed hydroformylation of *N*-allylpyrroles,[10] (c) based on organosulfur and selenium chemistry (i.e., conjugate addition of nitrogen nucleophiles containing ester or chloroalkyl substituents to acetylenic sulfones, followed by base-mediated intramolecular alkylation or acylation),[11] (d) by stereocontrolled cyclic nitrone cycloaddition,[12] (e) by addition of allylsilanes to *N*-acyliminium ions,[13] (f) by stereoselective conjugate addition reactions,[14] (g) through radical azidation reactions,[15] and (h) through chiral

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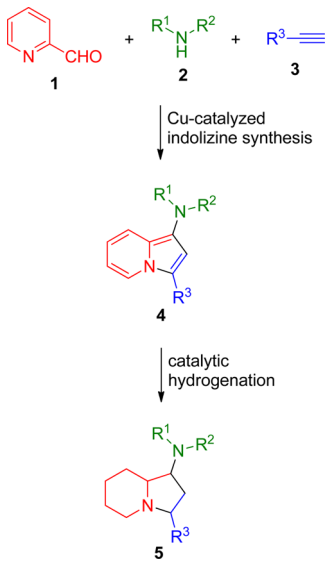
oxazolopiperidone lactams.[16] However, although the synthesis of indolizidines by the reduction of indolizines seems to be a direct approach, it has been barely documented and limited to some isolated examples.[17] Other reports describe the synthesis of indolizidines by heterogeneous catalytic hydrogenation of the pyrrole ring of 5,6,7,8-tetrahydroindolizines.[18] To the best of our knowledge, there is only one systematic study on the synthesis of indolizidines by full hydrogenation of indolizines, recently reported by Coelho et al.[19] At any rate, partial reduction is a common problem encountered, which together with a desirable higher diastereoselectivity[20] make the selective hydrogenation of indolizines a challenging objective.

On the other hand, multicomponent heterocyclic synthesis is an effectual strategy to build diverse and complex structures in a sole operation and atom-economic fashion.[21] Based on our interest and commitment to comprehend the reactivity of transition-metal colloids,[22] we present a catalyst composed of oxidized copper nanoparticles supported on activated carbon (CuNPs/C), which was easily obtained under soft conditions and is highly versatile in the multicomponent click synthesis of 1,2,3-triazoles in water using different azido precursors.[23] More recently, the same catalyst was shown to be effective in the multicomponent synthesis of indolizines from pyridine-2-carbaldehyde derivatives, secondary amines, and terminal alkynes.[24] In this work, we also introduce what is, to the best of our knowledge, the first example of a 1,3-disubstituted indolizidine bearing an amino group at the 1 position, obtained by catalytic hydrogenation of the corresponding indolizine.[24a] Herein, we present a complete survey on our efforts to develop a straightforward synthesis of 1-amino-3-substituted indolizidines based on the chemo- and diastereoselective catalytic hydrogenation of indolizines (Scheme 1).

Scheme 1. Synthetic Sequence toward 1-Amino 3-Substituted Indolizidines



RESULTS AND DISCUSSION

First, we optimized the catalyst and reaction conditions for the catalytic hydrogenation of indolizines. *N*,*N*-Dibenzyl-3-phenylindolizin-1-amine (**4h**) was chosen as the model substrate because its hydrogenation was considered more challenging due to the presence of three carbon−nitrogen bonds prone to undergo hydrogenolysis. In addition, the different hydrogenation degrees for the five- and six-membered rings of the indolizine nucleus made the desired transformation more difficult to achieve. In principle, all of the reactions were carried out at room temperature with 10 mol % of a platinum catalyst in different solvents or mixtures of solvents at various hydrogen pressures (Table 1); MeOH−CH_2Cl_2 or MeOH−HOAc mixtures favored solubilization of the starting indolizine with respect to the use of only MeOH. When PtO_2 was used as catalyst (Table 1, entries 1−14), higher pressure (3.7 atm) and shorter reaction time (2 h) increased the conversion into the desired indolizidine **5h**, particularly in the presence of HOAc as solvent (Table 1, entry 8); variable amounts of the monodebenzylated indolizidine **6h** and a semi-hydrogenation product (at this stage postulated to be **8h**) were also formed. Longer reaction time (8 h) at the same pressure had a detrimental effect on the conversion due to additional byproduct formation (Table 1, compare entries 8 and 9). The combination of HOAc with either MeOH or CH_2Cl_2 gave quite good results but did not improve those reached with PtO_2 (Table 1, entries 13 and 14). We then explored the behavior of different platinum-based supported catalysts. The highest conversions were achieved with Pt (5 wt %)/$CaCO_3$ and Pt (5 wt %)/C (Table 2, entries 18 and 24, respectively), as above, when pressure (3.7 atm) and short reactions time (3 h) were applied in HOAc, with the concomitant formation of **6h** and **8h**. As in the case of PtO_2 (Table 1, entry 11), lower catalyst loading (5 mol %) in the supported catalysts led to a decrease in the conversion though of a lower magnitude compared to the former (Table 1, entries 19 and 25).

Other metal catalysts were also tested with the aim to minimize byproduct formation (Table 2). Pd (10 wt %)/C provided a moderate conversion into **5h** at ambient pressure and prolonged stirring in MeOH, together with a substantial amount of monodebenzylated **6h** (Table 2, entry 1); higher hydrogen pressure shortened the reaction time but did not improve the conversion (Table 2, entry 2). An interesting effect of the pressure was noticed with Pd (20 wt %)/C in HOAc, leading to **6h** at 3.7 atm or **7h** at ambient pressure with some selectivity (Table 2, entries 4 and 5). Unfortunately, any possibility for directly transforming the starting indolizine **4h** into **6h** or **7h** by the choice of the pressure vanished because of the low diastereoselectivity attained in both cases (Table 2, footnotes d and g). This lack of diastereoselectivity was also manifested with the deployment of Pd (5 wt %)/$CaCO_3$ which, conversely, was highly chemoselective toward the formation of **6h** (Table 2, entry 7). Other catalysts, either heterogeneous [$Pd(OH)_2$/C, Rh(5 wt %)/C and Ru(5 wt %)/C] or homogeneous [$[Rh(COD)Cl]_2$, $[RuCl_2(p\text{-cymene})]_2$, $[Ir(COD)Cl]_2$], and/or reaction conditions furnished complex reaction mixtures (Table 2, entries 6, 8, 9, and 11), no product (Table 2, entries 12−14), or a certain amount of *N*-benzylidene-3-phenylindolizin-1-amine, i.e., the imine of monodebenzylated **6h** (Table 2, entries 3, 16, and 17).

From this optimization study it can be concluded that PtO_2 and Pt (5 wt %)/C are the best catalysts in terms of conversion and selectivity (Table 1, entries 8 and 24, respectively). Given the heterogeneous nature of both catalysts, they are potentially recoverable and recyclable.[25] PtO_2 could be easily reused by decantation, supernatant removal, and catalyst washing in the same hydrogenation flask. In contrast, further manipulation and centrifugation were required for Pt (5 wt %)/C. For comparative purposes, all recycling experiments were conducted at 3.7 atm for 2 h (Figure 1). Catalyst reutilization was found to be more efficient with PtO_2 than with Pt (5 wt %)/C (60% versus 36% in

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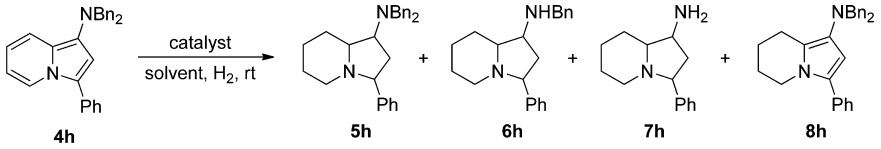
Table 1. Hydrogenation of Indolizine 4h Using Platinum Catalysts[a]



entry	catalyst	solvent	P (H_2, atm)	time (h)	**5h/6h/7h/8h**[b] (%)
1	PtO_2	MeOH−CH_2Cl_2[c]	1.0	72	47/−/−/−
2	PtO_2	MeOH−CH_2Cl_2[c]	3.7	2	44/7/−/6
3	PtO_2	EtOH	3.7	8	8/2/−/−
4	PtO_2	CH_2Cl_2	3.7	2	8/−/−/−
5	PtO_2	EtOAc	3.7	2	23/−/−/−
6	PtO_2	EtOAc	3.7	9	26/−/−/−
7	PtO_2	HOAc	1.0	24	39/−/−/−
8	**PtO_2**	**HOAc**	**3.7**	**2**	**65/2/−/21**
9	PtO_2	HOAc	3.7	8	26/10/−/5
10	PtO_2	HOAc	5.1	1	48/−/−/−
11	PtO_2[d]	HOAc	3.7	2	40/−/−/12
12	PtO_2	HOAc	1.0[e]	23	19/24/−/25
13	PtO_2	MeOH−HOAc[f]	3.7	2	53/−/−/20
14	PtO_2	CH_2Cl_2−HOAc[f]	3.7	2	65/13/−/10
15	Pt (1 wt %)/Al_2O_3	MeOH−CH_2Cl_2[c]	3.7	2	31/−/−/−
16	Pt (1 wt %)/Al_2O_3	HOAc	3.7	2	55/−/−/−
17	Pt (5 wt %)/Al_2O_3	HOAc	1.0[e]	20	−/−/−/−
18	**Pt (5 wt %)/$CaCO_3$**	**HOAc**	**3.7**	**3**	**62/14/−/14**
19	Pt (5 wt %)/$CaCO_3$[d]	HOAc	3.7	3	57/7/−/30
20	Pt (5 wt %)/$CaCO_3$	HOAc	1.0[e]	20	10/23/−/36
21	Pt (5 wt %)/SiO_2	HOAc	3.7	3	−/−/−/−
22	Pt (10 wt %)/C	MeOH−CH_2Cl_2[c]	3.7	4	24/−/−/−
23	Pt (10 wt %)/C	HOAc	3.7	2	56/−/−/−
24	**Pt (5 wt %)/C**	**HOAc**	**3.7**	**3**	**68/6/−/8**
25	Pt (5 wt %)/C[d]	HOAc	3.7	3	52/7/−/15
26	Pt (5 wt %)/C	HOAc	1.0[e]	23	16/19/−/9
27	Pt (5 wt %)/C	HOAc	1.0[e]	7[g]	30/14/−/26
28	Pt (5 wt %)/C	HOAc	1.0[e]	48[g]	22/46/−/−
29	Pt (5 wt %)/C	MeOH−HOAc[c]	3.7	3	9/5/−/−

[a]Reaction conditions: **4h** (0.3 mmol), catalyst (10 mol %), solvent (3.0 mL), and H_2 at rt. [b]Conversion determined by GLC. [c]3:1 v/v. [d]5 mol %. [e]Balloon. [f]1:1 v/v. [g]Reaction at 50 °C.

the second cycle). The catalytic activity of both catalysts decreased in subsequent cycles: 35 and 30% for PtO_2 and <10% for Pt (5 wt %)/C, although better conversions would be expected for longer reaction times. In addition to this, we also observed that the catalytic performance of Pt (5 wt %)/C with substrates other than **4h** was lower than with PtO_2.[26] In view of the aforementioned results, the catalytic system of choice was that composed of PtO_2 (10 mol %) in HOAc at 3.7 atm H_2 (Table 1, entry 8).

In order to study the substrate scope, the optimized catalyst and reaction conditions were applied to a variety of indolizines **4** derived from pyridine-2-carbaldehyde (**1a**), secondary amines (**2**), and terminal alkynes (**3**), producing the expected indolizidines **5** in modest to high yields and with high to excellent diastereoselectivity (Table 3). The yield and diastereoselectivity were found to be dependent on the substituents at the 1 and 3 positions, with the amino group at the 1 position apparently exerting a stronger effect. For instance, the indolizines derived from piperidine and arylacetylenes were isolated in lower yields, with the lowest diastereoselectivity recorded for the phenylacetylene derivative (**5a**). The diastereomeric ratio was improved when a *para* substituent was present in the arylacetylene-derived moiety while at the same time maintaining the 1-piperidinyl group (Table 3, compare **5a** with **5b** and **5c**). Fortunately, purification by column chromatography allowed the isolation of **5a** and **5b** as single diastereoisomers. Better yield and excellent diastereoselectivity were observed when the 1-piperidinyl was changed into a 1-morpholino group (Table 3, compare **5a** with **5d**). In general, the results with acyclic amines were better than those with the cyclic counterparts concerning the yield, the diastereoselectivity, and the reaction time. The diastereoselectivity increased when the steric hindrance of the secondary amine was increased (Table 3, compare **5e** and **5f** with **5g** and **5h**). The indolizidines derived from dibenzylamine followed a trend similar to that of dibutylamine (**5g**), being generally obtained in relatively short hydrogenation reaction times and as single diastereoisomers (Table 3, **5h−m**). This remarkable behavior was displayed irrespective of the substituent at the 3 position of the indolizidine nucleus, including aryl substituents with electron-neutral (Table 3, **5h** and **5i**), -releasing (Table 3, **5j**), and -withdrawing groups (Table 3, **5k** and **5l**) as well as aliphatic substituents (Table 3, **5m**).

We endeavored to extend this method to more demanding indolizines in order to validate its applicability. Such is the case of *N*,*N*-dibutyl-1-phenylpyrrolo[1,2-*a*]quinolin-3-amine (**4n**), a benzo-fused indolizine coming from the coupling of quinoline-

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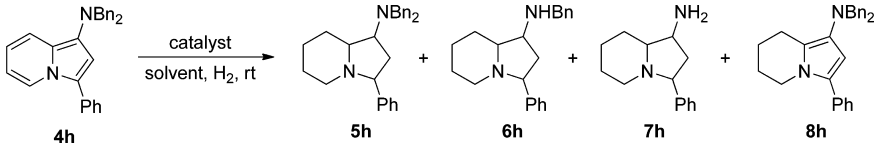
Table 2. Hydrogenation of Indolizine 4h Using Other Metal Catalysts[a]



entry	catalyst	solvent	P (H_2, atm)	time (h)	**5h**/**6h**/**7h**/**8h**[b] (%)
1	Pd (10 wt %)/C	MeOH	1.0	48	64/19/−/−
2	Pd (10 wt %)/C	MeOH	3.7	7	48/4/−/−
3	Pd (10 wt %)/C	HOAc	3.7	2	−[c]
4	Pd (20 wt %)/C	HOAc	3.7	3	−/92[d]/8/−
5	Pd (20 wt %)/C	HOAc	1.0[e]	23	−/16[f]/64[g]/−
6	Pd (5 wt %)/$CaCO_3$	HOAc	3.7	3	−[h]
7	Pd (5 wt %)/$CaCO_3$	HOAc	1.0[e]	20	−/81[i]/−/−
8	$Pd(OH)_2$/C	MeOH	1.0	22	−[h]
9	$Pd(OH)_2$/C	MeOH−CH_2Cl_2[j]	1.0	13	−[h]
10	$Pd(OH)_2$/C	MeOH−CH_2Cl_2[j]	3.7	6	−/27/−/−
11	$Pd(OH)_2$/C	MeOH−CH_2Cl_2[k]	1.0	15	−[h]
12	Rh (5 wt %)/C	HOAc	1.0[e]	20	−
13	Rh (5 wt %)/C	HOAc	3.7	3.5	−
14	Ru (5 wt %)/C	HOAc	3.7	4	−
15	$[Rh(COD)Cl]_2$	MeOH−CH_2Cl_2[j]	3.7	10	−[l]
16	$[RuCl_2(p\text{-cymene})]_2$	*i*-PrOH	3.7	8	−[m]
17	$[Ir(COD)Cl]_2$	HOAc	3.7	8	−[n]

[a]Reaction conditions: **4h** (0.3 mmol), catalyst (10 mol %), solvent (3.0 mL), and H_2 at rt. [b]Conversion determined by GLC. [c]Monodebenzylated **4h** (25%) and its imine (35%). [d]55:45 dr. [e]Balloon. [f]62:38 dr. [g]64:19:17 dr. [h]Complex mixture. [i]47:44:9 dr. [j]MeOH−CH_2Cl_2 (3:1 v/v). [k]MeOH−CH_2Cl_2 (1:1 v/v). [l]Unidentified product (29%). [m]Imine of monodebenzylated **4h** (12%). [n]Imine of monodebenzylated **4h** (4%).

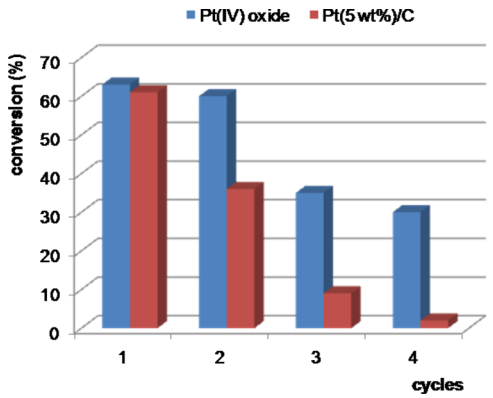


Figure 1. Catalyst recycling experiments in the hydrogenation of **4h** (3.7 atm H_2, 2 h).

2-carbaldehyde (**1b**), dibutylamine (**2e**), and phenylacetylene (**3a**). It is worthy of note that its catalytic hydrogenation failed under the standard pressure and that a slightly higher pressure was necessary to initiate the reaction. Consequently, the latter was found to be more chemoselective at lower than at higher conversions, with an increase of byproduct formation in the second case. The scant yield of the expected hexahydropyrrolo[1,2-*a*]quinolin-3-amine **5n** was compensated for by the high diastereomeric ratio reached; the presence of the fused benzene in the tricyclic indolizine core did not vary the stereochemical outcome with respect to the bicyclic counterparts. We went one step further by dealing with the hydrogenation of the trisubstituted indolizine **4o**, the precursors of which were 6-methylpyridine-2-carbaldehyde (**1c**), dibenzylamine (**2f**), and phenylacetylene (**3a**). In this case, a short reaction time was more convenient to minimize byproduct formation. It was gratifying to know that, though in modest isolated yield, the four-stereocenter indolizidine **5o** could be obtained with very high diastereoselectivity.

In some cases, byproducts derived from the partial hydrogenation of the indolizine nucleus were detected in minor amounts. This fact, together with the relative high polarity of the indolizidines, made purification by column chromatography troublesome and accounted for some of the lower isolated yields recorded.

We were delighted to confirm that the indolizidine **5h** could be obtained from pyridine-2-carbaldehyde (**1a**), dibenzylamine (**2f**), and phenylacetylene (**3a**) without the need to isolate the intermediate indolizine (avoiding the corresponding workup and purification) in a slightly higher yield than that obtained from the isolated indolizine (70 versus 65%, Scheme 2). Therefore, this method represents a straightforward access into a new type of stereodefined indolizidines with three (or four) stereocenters.

Secondary amines are versatile nitrogenated compounds with multiple applications in organic chemistry as, for example, organocatalysts,[27] Lewis bases (e.g., for the activation of electron-deficient olefins),[28] or building scaffolds for multicomponent reactions,[29] among many others. On the other hand, in organic chemistry, it is desirable that the selective conversion of a single starting material into two or more different products can be accomplished by the selection of the catalyst.[30] In this vein, attempts to directly transform indolizine **4h** into the monobenzylated secondary amine **6h** were found to be successful in terms of conversion under palladium catalysis; regretfully, the diastereoselectivity of these reactions was too low (Table 2, entries 4 and 7, footnotes d and i). We then decided to take advantage of the presence of two benzyl groups in the indolizidines **5h**−**m**,**o** to investigate the possibilities of effecting selective hydrogenolyses, leading to secondary amines **6** or primary amines **7**, through mono- and didebenzylation processes, respectively.

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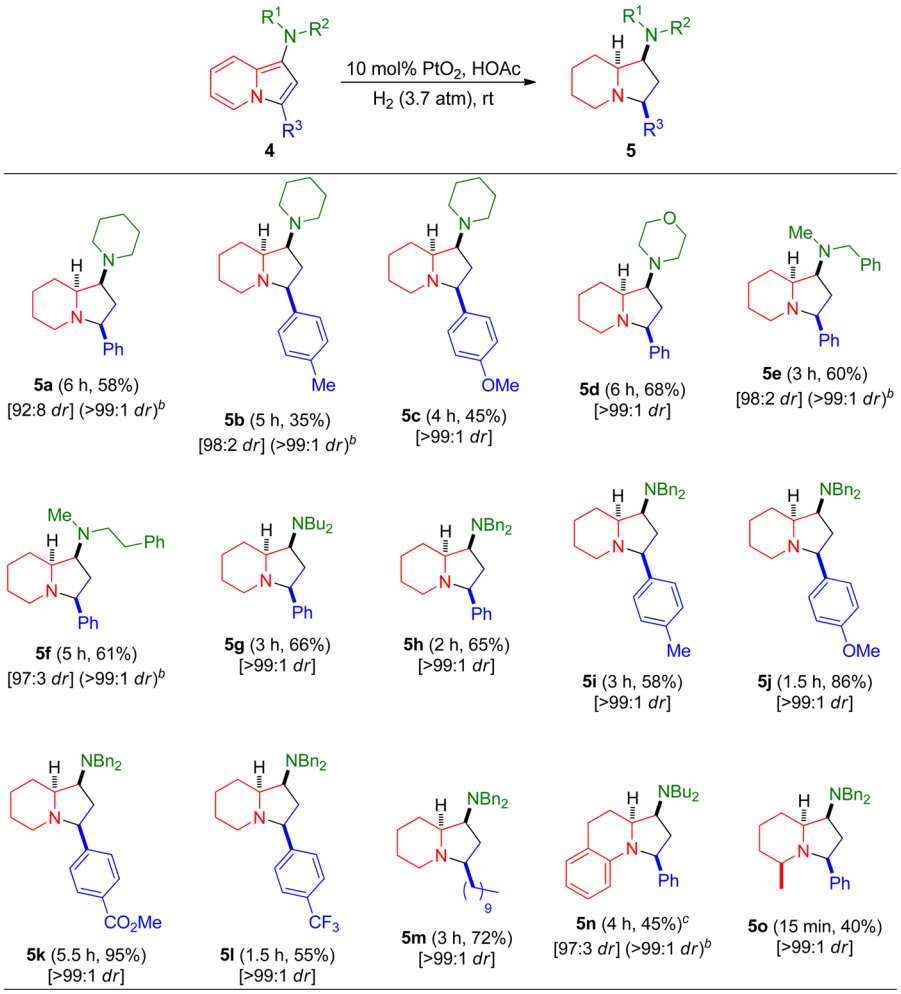
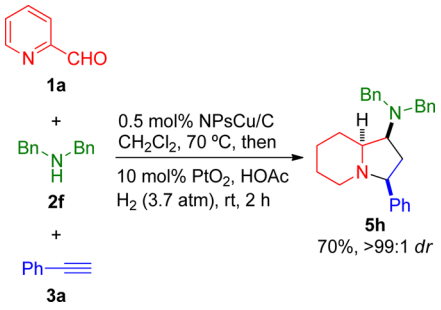
Table 3. Synthesis of the Indolizidines 5[a]



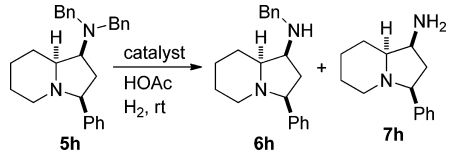
[a]Reaction conditions: **4** (0.5 mmol), PtO_2 (10 mol %), HOAc (3 mL), H_2 (3.7 atm), rt; reaction time and isolated yield in parentheses; diastereomeric ratio in brackets determined by GC–MS from the reaction crude. [b]Diastereomeric ratio after purification by column chromatography. [c]Reaction at 4.1 atm.

Scheme 2. One-Pot-Type Synthesis of Indolizidine 5h



Taking into account the information in Tables 1 and 2, four catalysts were considered for this study, including platinum and palladium catalysts, using indolizidine **5h** as the starting material (Table 4). As a general trend, platinum catalysts provided the monodebenzylated product **6h**, whereas the palladium catalyst favored the full debenzylated product **7h**. A significant effect of the hydrogen pressure was also discerned, with ambient pressure resulting in higher conversions and less formation of side products. Prolonged stirring was recommended in both cases because that did not alter the high selectivity attained with the platinum catalysts [Pt (5 wt %)/C and PtO_2] (Table 4, entries 3 and 4) and guaranteed the full hydrogenolysis with Pd (20 wt %)/C (Table 4, compare entries 7 and 8).

Table 4. Optimization of the Hydrogenolysis of 5h[a]



entry	catalyst	*P* (H_2, atm)	time (h)	**6h**/**7h**[b] (%)
1	Pt (5 wt %)/C	3.7	2	15/–
2	Pt (5 wt %)/C	3.7	6	31/–
3	**Pt (5 wt %)/C**	**1.0**[c]	**22**	**61**/–
4	**PtO_2**	**1.0**[c]	**17**	**83**/–
5	Pt (5 wt %)/$CaCO_3$	1.0[c]	16	59/–
6	Pd (20 wt %)/C	3.7	2	31/–
7	Pd (20 wt %)/C	1.0[c]	7	6/77
8	**Pd (20 wt %)/C**	**1.0**[c]	**23**	**–/82**

[a]Reaction conditions: **5h** (0.3 mmol), catalyst (10 mol %), HOAc (3.0 mL), and H_2 at rt. [b]Conversion determined by GLC. [c]Balloon.

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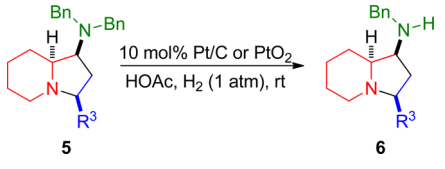
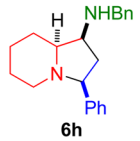
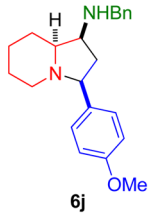
Table 5. Mono-debenzylation of Indolizidines 5[a]

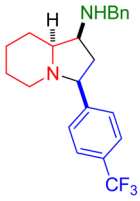




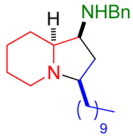
6h
17 h, 68%[b]
>99:1 *dr*



6j
24 h, 72%[b]
>99:1 *dr*



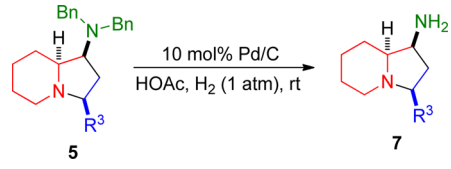
6l
19 h, 65%[c]
>99:1 *dr*

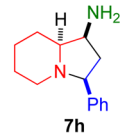


6m
23 h, 81%[c]
>99:1 *dr*

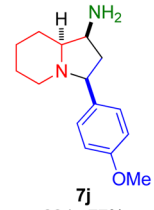
[a]Reaction conditions: **5** (0.3 mmol), catalyst (10 mol %), HOAc (3.0 mL), and H_2 (1 atm) at rt; isolated yield after purification by preparative TLC (hexane/EtOAc 6:4); conversions into **6** were in the range 82 → 99%); diastereomeric ratio determined by GC–MS from the reaction crude. [b]Reaction catalyzed by PtO_2. [c]Reaction catalyzed by Pt (5 wt %)/C.

Table 6. Di-debenzylation of indolizidines 5[a]

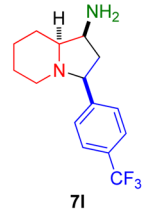




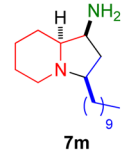
7h
23 h, 85%
>99:1 *dr*



7j
22 h, 77%
>99:1 *dr*



7l
16 h, 74%
>99:1 *dr*



7m
22 h, 92%
>99:1 *dr*

[a]Reaction conditions: **5** (0.3 mmol), Pd (20 wt%)/C (10 mol %), HOAc (3.0 mL), and H_2 (1 atm) at rt; conversions into **7** were in the range 73 → 99%. Compounds **7h** and **7l** were purified by preparative TLC (EtOAc). Compounds **7j** and **7m** did not require any further purification. Diastereomeric ratio determined by GC–MS from the reaction crude.

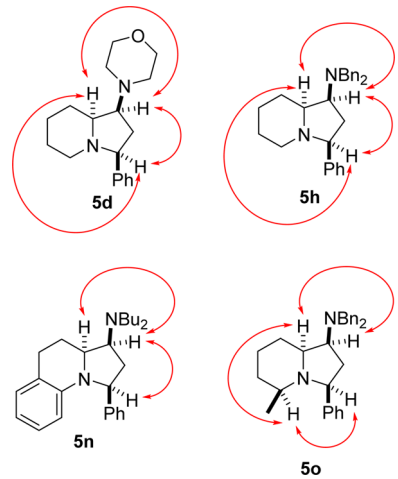


Figure 2. Selected $^1H–^1H$ correlations from NOESY experiments.

The optimized conditions were first applied to the selective monodebenzylation of some of the indolizidines **5h–m**. As representative examples, indolizidines derived from aromatic alkynes of diverse electronic nature (neutral, rich, and deficient ones), as well as from aliphatic alkynes, were converted into the monobenzylated counterparts **6** in moderate to high yields (Table 5). Although both catalysts, PtO_2 and Pt (5 wt %)/C, selectively catalyzed the monodebenzylation reaction at ambient hydrogen pressure and temperature, the yields were slightly higher when the former was utilized for **5h** and **5j** and the latter for **5l** and **5m**.

When the same substrates, as above, were submitted to hydrogenolysis catalyzed by Pd (20 wt %)/C at ambient hydrogen pressure and temperature, the corresponding free aminoindolizidines **7** were produced in high yields as a result of a di-debenzylation process (Table 6). It is noteworthy that the original stereochemical integrity of the indolizidines was unaffected during the hydrogenolyses leading to the desired products as single diastereomers.

The stereochemistry of the indolizidines **5** was originally proposed on the basis of 2D-NMR experiments conducted for **5d**, **5h**, **5n**, and **5o** (Figure 2) and, later on, unequivocally established by X-ray crystallographic analysis of compound **5a** (Figure 3).[31] In view of these data, the major diastereoisomer obtained in the catalytic hydrogenation of the indolizines is that resulting from the addition of hydrogen to the same face of the indolizine nucleus.

Finally, we were intrigued to know about the hydrogenation pathway and the structure of any possible semihydrogenated intermediate. With this purpose in mind, indolizine **4a** was hydrogenated under the standard conditions but for a shorter reaction time. These intermediates were found to be rather elusive because of their minor formation and high tendency toward overhydrogenation. Notwithstanding these added difficulties, we managed to isolate a certain amount of the 5,6,7,8-tetrahydroindolizine **8a**, which confirmed the preferential hydrogenation of the six-membered ring of the indolizine nucleus. Further hydrogenation of **8a** gave rise to the fully reduced indolizidine **5a** with the same stereoselectivity as above. These results lend weight to the argument that the stereochemistry of the indolizidines is fixed in a second stage, where all hydrogen atoms are delivered from the catalyst to the same face of the pyrrole ring in **8a** (Scheme 3).

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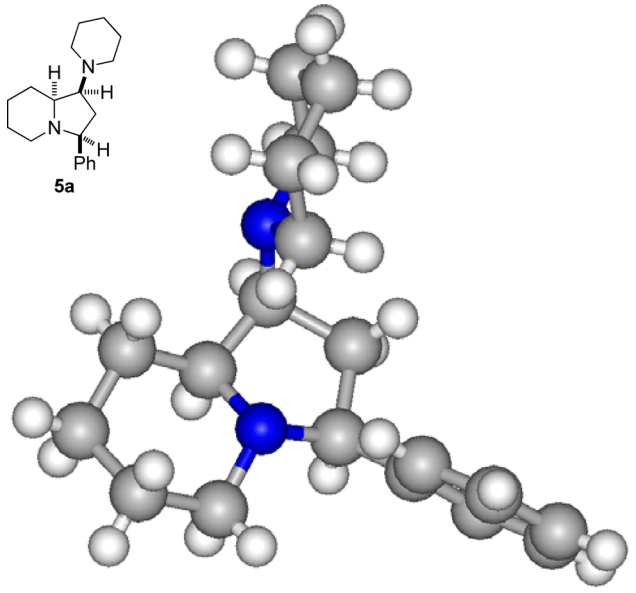
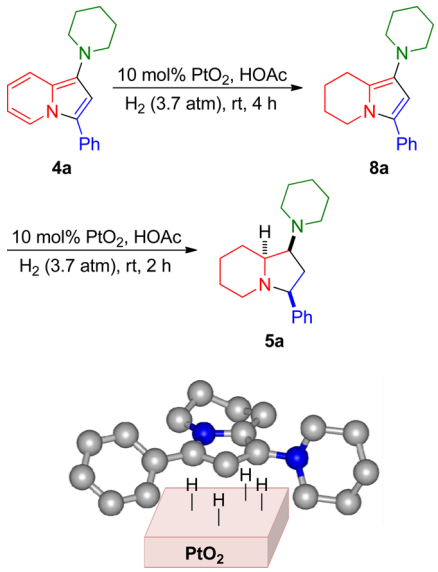


Figure 3. X-ray structure of compound **5a**.

Scheme 3. Sequential Hydrogenation of the Indolizine 4a and Hydrogenation Model of 8a



CONCLUSION

A series of 1-amino substituted indolizidines have been synthesized from readily available indolizines by heterogeneous catalytic hydrogenation. By the choice of the catalyst (PtO_2, Pt/C or Pd/C), tertiary, secondary, or primary amino-substituted indolizidines are selectively produced in modest to excellent yields (35−95%), mostly as single diastereomers (with three or four stereocenters). Experimental evidence supports the indolizine hydrogenation occurring through the pyrrolic intermediate 5,6,7,8-tetrahydroindolizine. Furthermore, the indolizidine synthesis can be sequentially and successfully implemented by the copper-catalyzed multicomponent synthesis of the indolizine nucleus followed by the platinum-catalyzed heterogeneous hydrogenation, without the need to isolate the intermediate indolizine. This approach represents a direct pathway to a new type of indolizidines.

EXPERIMENTAL SECTION

General Methods. Platinum(IV) oxide, Pt (5 wt %)/C, and Pd (20 wt %)/C were commercially available. Catalytic hydrogenation was carried out in a Parr hydrogenation apparatus using a 500 mL flask. Melting points are uncorrected. Infrared analysis was performed with a FT-IR spectrophotometer equipped with an ATR component; wavenumbers are given in cm^{-1}. NMR spectra were recorded at 300 or 400 MHz for ^1H NMR and 75 and 101 MHz for ^{13}C NMR; chemical shifts are given in (δ) parts per million and coupling constants (J) in hertz. Mass spectra (EI) were obtained at 70 eV with a GC−MS apparatus; fragment ions are presented in m/z with relative intensities (%) in parentheses. HRMS analyses were carried out in the electron-impact mode (EI) at 70 eV using a quadrupole analyzer or with a LC-ESI-TOF system. Elemental analysis was performed on a CHNS microanalyzer. X-ray data collection was based on three ω-scan runs (starting $\omega = -34°$) at values of $\phi = 0°$, 120°, and 240° with the detector at $2\theta = -32°$. An additional run at $\phi = 0°$ of 100 frames was collected to improve redundancy. The diffraction frames were integrated using the SAINT program, and the integrated intensities were corrected for Lorentz-polarization effects with SADABS.[32] The purity of volatile compounds and the chromatographic analyses (GLC) were determined with a gas chromatograph equipped with a flame ionization detector and a 30 m capillary column (0.32 mm diameter, 0.25 μm film thickness), using nitrogen (2 mL/min) as carrier gas, $T_{injector}$ = 270 °C, T_{column} = 60 °C (3 min) and 60−270 °C (15 °C/min); retention times (t_R) are given in min. Thin-layer chromatography was carried out on TLC aluminum sheets covered with silica gel. Column chromatography was performed using silica gel of 40−60 μm (hexane/EtOAc as eluent). Preparative thin-layer chromatography was carried on laboratory-made TLC glass plates with silica gel 60 PF_{254} (hexane/EtOAc or EtOAc).

General Procedure for the Synthesis of the Indolizines 4. The indolizines **4** were prepared from pyridine-2-carbaldehyde derivatives, secondary amines, and terminal alkynes according to our previously published procedure.[24] The aldehyde (**1**, 0.5 mmol), amine (**2**, 0.5 mmol), and alkyne (**3**, 0.5 mmol) were added to a reactor tube containing CuNPs/C (20 mg, ca. 0.5 mol %) and dichloromethane (1.0 mL). The reaction mixture was warmed to 70 °C without the exclusion of air and monitored by TLC and/or GLC until total or steady conversion of the starting materials. The solvent was removed in vacuo; EtOAc (2 mL) was added to the resulting mixture followed by filtration through Celite and washing with additional EtOAc (4 mL). The reaction crude obtained after evaporation of the solvent was purified by column chromatography (silica gel, hexane/EtOAc) to give the corresponding indolizine **4**. The physical and spectroscopic data of the new indolizine **4o** follow:

*N,N-Dibenzyl-5-methyl-3-phenylindolizin-1-amine (**4o**):* yellow oil (247 mg, 61%); t_R 29.11; R_f 0.73 (hexane/EtOAc, 8:2); IR (neat) ν 3079, 3066, 3027, 2925, 2827, 1599, 1492, 1472, 1451, 1292, 1070, 748, 696; ^1H NMR (300 MHz, $CDCl_3$) δ 2.01(s, 3H), 4.17 (s, 4H), 6.13 (d, J = 6.5 Hz, 1H), 6.48 (dd, J = 8.8, 6.5 Hz, 1H), 6.55 (s, 1H), 7.14−7.29 (m, 11H), 7.37 (d, J = 7.0 Hz, 1H), 7.49 (d, J = 8.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0, 59.4, 111.4, 111.9, 114.7, 115.6, 126.7, 126.8, 127.0, 128.0, 128.6, 130.9, 123.5, 127.2, 134.0, 136.0, 139.6; MS (EI) m/z 402 (M^+, 0.3), 311 (23), 310 (99), 309 (39), 295 (10), 281 (18), 221 (10), 209 (13), 208 (24), 207 (100), 191 (17), 91 (26); HRMS (ESI) m/z $[M]^+$ calcd for $C_{29}H_{26}N_2$ 402.2096, found 402.2093.

General Procedure for the Optimization of the Catalytic Hydrogenation. A suspension of the indolizine **4h** (0.3 mmol) and catalyst (0.03 mmol) in glacial HOAc (3 mL) was hydrogenated at different pressures and reaction times, at room temperature, as indicated in Tables 1 and 2. The catalyst was removed by filtration, and the resulting mixture was diluted with EtOAc and analyzed by GLC, TLC, and GC−MS.

General Procedure for the Hydrogenation of Indolizines 4 Catalyzed by PtO_2. The indolizine **4** (0.5 mmol) was poured into the hydrogenation flask followed by the addition of PtO_2 (11.4 mg, 10 mol %) and glacial HOAc (3 mL), with this mixture being subjected to hydrogenation at 3.74 atm (55 psi) and ambient temperature. The reaction was monitored by TLC and/or GLC until total or steady conversion of the starting material (see Table 2). The catalyst was

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separated by filtration, and the solvent was removed under vacuum. Purification of the reaction crude by column chromatography (silica gel, hexane/EtOAc) afforded the pure indolizidines **5** as single diastereoisomers.

(1R,3R*,8aR*)-3-Phenyl-1-(piperidin-1-yl)octahydroindolizine (**5a**):* yellow solid (83 mg, 58%); t_R 12.62; R_f 0.40 (hexane/EtOAc, 4:6); mp 68.9−70.9 °C (EtOH); IR (neat) ν 3084, 3050, 3030, 2929, 2851, 2789, 2789, 1601, 1439, 1364, 1260, 1142, 1126, 1105, 863, 755, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13−1.26, 1.34−1.66, 1.71−1.85, 1.98−2.11, 2.29−2.40, 2.67−2.86, 3.11−3.32 (7m, 22H), 2.96 (t, J = 8.7 Hz, 1H), 7.19−7.25, 7.28−7.44 (2m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.7, 24.8, 25.6, 26.3, 26.6, 31.7, 51.7, 52.9, 65.3, 68.9, 70.2, 126.8, 127.4, 128.4, 143.8; MS (EI) m/z 284 (M^+, 9), 201 (13), 174 (10), 173 (76), 172 (100), 110 (44); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{29}N_2$ 285.2341, found 285.2331.

(1R,3R*,8aR*)-1-(Piperidin-1-yl)-3-p-tolyloctahydroindolizine (**5b**):* brown oil (52 mg, 35%); t_R 13.14; R_f 0.40 (hexane/EtOAc, 1:1); IR (neat) ν 3046, 3009, 2927, 2851, 2786, 2747, 1512, 1439, 1260, 1143, 1126, 1105, 1036, 863, 813, 797, 735; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15−1.86 (m, 14H), 1.92−2.08 (m, 2H), 2.27−2.40 (m, 5H), 2.63−2.86 (m, 3H), 2.92 (t, J = 8.7 Hz, 1H), 3.16 (ddd, m, J = 9.0 Hz, 7.4, 3.8, 1H), 7.12 (d, J = 7.8 Hz, 2H), 7.23 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 24.8, 24.9, 25.6, 26.4, 26.6, 31.7, 51.8, 52.9, 65.4, 69.0, 70.0, 127.3, 129.1, 136.3, 140.9; MS (EI) m/z 298 (M^+, 6), 215 (12), 188 (10), 187 (71), 186 (100), 110 (45); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{31}N_2$ 299.2487, found 299.2500.

(1R,3R*,8aR*)-3-(4-Methoxyphenyl)-1-(piperidin-1-yl)-octahydroindolizine (**5c**).* This compound was isolated together with an inseparable impurity as a brown oil (71 mg, approximately 45%): t_R 14.20; R_f 0.42 (hexane/EtOAc, 4:6); IR (neat) ν 3060, 2991, 2930, 2852, 2785, 2749, 1611, 1509, 1439, 1300, 1242, 1179, 1170, 1143, 1126, 1101, 1036, 828, 798; *Selected NMR data:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06−1.91 (m, 15H), 1.94−2.09 (m, 2H), 2.26−2.49 (m, 2H), 2.73−2.81 (m, 2H), 2.91 (t, J = 8.7 Hz, 1H), 3.12−3.30 (m, 1H), 3.80 (s, 3H), 6.84−6.89 (m, 2H), 7.21−7.32 (m, 2H); ^{13}CNMR (101 MHz, $CDCl_3$) δ 24.7, 24.8, 25.6, 26.2, 26.6, 31.7, 51.7, 52.8, 55.4, 65.2, 68.9, 69.7, 113.8, 128.4, 135.8, 158.6; MS (EI) m/z 314 (M^+, 6), 231 (15), 204 (11), 203 (76), 202 (100), 110 (47); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{31}N_2O$ 315.2436, found 315.2435.

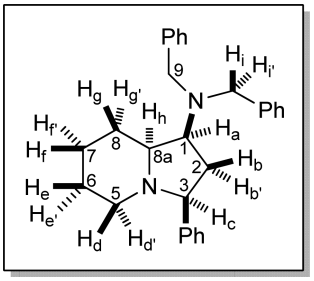
4-[(1R,3R*,8aR*)-3-Phenyloctahydroindolizin-1-yl]morpholine (**5d**):* yellow solid (97 mg, 68%); t_R 12.69; R_f 0.34 (hexane/EtOAc, 8:2); mp 53.7−55.7 °C (EtOH); IR (neat) ν 3079, 3060, 3030, 2939, 2849, 2802, 2749, 1603, 1448, 1258, 1136, 1114, 998, 866, 755, 699; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16−1.28, 1.34−1.38, 1.50−1.69, 1.71−1.88, 2.00−2.12, 2.31−2.51, 2.73−2.91 (7m, 15H; 7 × CH_2, CH), 2.30 (t, J = 8.7 Hz, 1H; CH), 3.06−3.23 (m, 1H; CH), 3.66−3.77 (m, 4H; 2 × CH_2), 7.21−7.36 (m, 5H; 5 × ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 25.6, 26.7, 31.8, 51.1, 52.9, 67.4 (9 × CH_2), 65.1, 68.9, 70.2 (3 × CH), 126.9, 127.3, 128.5 (5 × ArCH), 143.5 (ArC); MS (EI) m/z 286 (M^+, 3), 203 (14), 173 (71), 172 (100), 112 (41), 104 (10). Anal. Calcd for $C_{18}H_{26}N_2O$: C, 75.48; H, 9.15; N, 9.78. Found: C, 75.88; H, 9.28; N 9.94.

(1R,3R*,8aR*)-N-Benzyl-N-methyl-3-phenyloctahydroindolizin-1-amine (**5e**):* brown oil; t_R 14.14 (96 mg, 60%); R_f 0.57 (hexane/EtOAc, 8:2); IR (neat) ν 3084, 3065, 3025, 2934, 2858, 2784, 1599, 1492, 1449, 1361, 1262, 1147, 1099, 1071, 1019, 867, 755, 731, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14−1.27, 1.36−1.48, 1.49−1.61, 1.69−1.80, 1.81−1.95, 2.10−2.19 (6m, 10H), 2.33 (s, 3H), 2.84 (d, J = 10.6 Hz, 1H), 3.02 (t, J = 8.7 Hz, 1H), 3.34−3.47 (d, m, J = 13.8 Hz, 2H), 4.10 (d, J = 13.8 Hz, 1H), 7.22−7.26, 7.28−7.40 (2m, 10H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.8, 25.5, 26.7, 32.1, 52.8, 59.0, 39.9, 63.1, 69.0, 70.1, 126.9, 127.0, 127.4, 128.4, 128.5, 128.9, 139.4, 143.5; MS (EI) m/z 320 (M^+, 2), 237 (13), 173 (76), 172 (100), 146 (46), 91 (35); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{22}H_{29}N_2$ 321.2335, found 321.2331.

(1R,3R*,8aR*)-N-Methyl-N-phenethyl-3-phenyloctahydroindolizin-1-amine (**5f**):* brown oil; t_R 15.50 (102 mg, 61%); R_f 0.66 (hexane/EtOAc, 4:6); IR (neat) ν 3084, 3065, 3025, 2933, 2848, 2784, 2749, 1603, 1493, 1451, 1362, 1262, 1144, 1100, 1029, 934, 867, 802, 755, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19−1.89, 2.04−2.18 (2m, 10H), 2.42 (s, 3H), 2.44−2.63, 2.73−2.85, 2.94−3.11, 3.25−3.42 (4m, 7H), 7.15−7.36 (m, 10H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.8, 25.7, 26.9, 32.8, 35.0, 52.8, 57.2, 40.1, 64.1, 69.2, 70.1, 125.9, 126.9, 127.4, 128.3, 128.4, 128.9, 141.1, 143.6; MS (EI) m/z 334 (M^+, 1), 251 (11), 243 (39), 173 (70), 172 (100), 160 (42), 139 (10), 91 (11); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{31}N_2$ 335.2487, found 335.2490.

(1R,3R*,8aR*)-N,N-Dibutyl-3-phenyloctahydroindolizin-1-amine (**5g**):* brown oil (108 mg, 66%); t_R 12.74; R_f 0.54 (hexane/EtOAc, 8:2); IR (neat) ν 3060, 3025, 2936, 2852, 2792, 1601, 1492, 1451, 1363, 1263, 1145, 1027, 976, 755, 741, 731, 696; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 6H), 1.14−1.87, 2.01−2.15, 2.18−2.36, 2.75−2.86, (4m, 23H), 2.94 (t, J = 8.7 Hz, 1H), 3.29−3.45 (m, 1H), 7.19−7.25 (m, 1H), 7.28−7.38 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 20.9, 25.0, 25.8, 27.1, 31.1, 34.1, 52.2, 52.8, 60.7, 69.5, 70.3, 126.8, 127.5, 128.4, 144.0; MS (EI) m/z 328 (M^+, 4), 174 (10), 173 (84), 172 (100), 154 (40), 140 (10), 117 (10), 91 (11); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{22}H_{37}N_2$ 329.2961, found 329.2957.

(1R,3R*,8aR*)-N,N-Dibenzyl-3-phenyloctahydroindolizin-1-amine (**5h**):* brown oil (129 mg, 65%); t_R 21.06; R_f 0.89 (hexane/EtOAc, 8:2); IR ν 3060, 3025, 2936, 2852, 2792, 1601, 1492, 1451, 1363, 1263, 1145, 1027, 976, 755, 741, 731, 696; ^{1}HNMR (300 MHz, $CDCl_3$) δ 1.14−1.25 (m, 1H; H_f), 1.34−1.44 (m, 1H; $H_{e'}$), 1.46−1.59 (m, 2H; H_e, $H_{d'}$), 1.75−1.87 (m, 3H; H_b, $H_{f'}$, H_g), 1.88−1.95 (m, 1H; $H_{g'}$), 1.99−2.08 (m, 1H; H_h), 2.08−2.19 (m, 1H; $H_{b'}$), 2.81 (d, J = 10.4 Hz, 1H; H_d), 2.98 (t, J = 8.8 Hz, 1H; H_c), 3.28 (d, J = 14.8 Hz, 2H; 2 × H_i), 3.36 (td, J = 8.8, 4.0 Hz, 1H; H_a), 4.20 (br s, 2H; 2 × $H_{i'}$), 7.19−7.27 (m, 3H; 3 × ArH), 7.28−7.40 (m, 8H; 8 × ArH), 7.41−7.51 (m, 4H; 4 × ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.8 (C-6), 25.6 (C-7), 27.0 (C-8), 32.4 (C-2), 52.9 (C-5), 56.1 (2 × C-9), 58.5 (C-1), 69.1 (C-8a), 70.2 (C-3), 126.7, 126.9, 127.4, 128.4, 128.5 (15 × ArCH), 140.8, 143.7 (3 × ArC); MS (EI) m/z 396 (M^+, 0.3), 306 (14), 305 (59), 222 (51), 174 (10), 173 (79), 172 (100), 117 (12), 91 (72); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{28}H_{32}N_2$ 396.2565, found 396.2585.



(1R,3R*,8aR*)-N,N-Dibenzyl-3-p-tolyloctahydroindolizin-1-amine (**5i**):* brown oil (119 mg, 58%); t_R 22.80; R_f 0.86 (hexane/EtOAc, 8:2); IR (neat) ν 3079, 3060, 3030, 2935, 2858, 2794, 2754, 1603, 1493, 1451, 1362, 1263, 1145, 813, 770, 740, 728, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14−1.56, 1.75−1.96, 1.99−2.16 (3 m, 10H), 2.35 (s, 3H), 2.80 (d, J = 10.6 Hz, 1H), 2.94 (t, J = 8.7 Hz, 1H), 3.28 (d, J = 14.5 Hz, 2H), 3.31−3.40 (m, 1H), 4.19 (broad s, 2H), 7.12−7.16, 7.19−7.25, 7.25−7.34, 7.41−7.53 (4m, 14H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.3, 24.8, 25.6, 27.0, 32.4, 52.9, 56.1, 58.5, 69.1, 69.9, 126.7, 127.3, 128.3, 128.5, 129.2, 136.5, 140.7, 140.8; MS (EI) m/z 410 (M^+, 0.2), 320 (10), 319 (41), 236 (31), 222 (10), 188 (11), 187 (77), 186 (97), 131 (12), 118 (14), 117 (11), 106 (10), 105 (27), 91 (100); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{29}H_{35}N_2$ 411.2800, found 411.2813.

(1R,3R*,8aR*)-N,N-Dibenzyl-3-(4-methoxyphenyl)-octahydroindolizin-1-amine (**5j**):* brown oil (183 mg, 86%); t_R 31.39; R_f 0.26 (hexane/EtOAc, 8:2); IR (neat) ν 3060, 3025, 2934, 2851, 2832, 2791, 2752, 1610, 1509, 1242, 1170, 1145, 1101, 1036, 828, 740, 728, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11−1.55, 1.76−2.15 (2m, 10H), 2.79 (d, J = 10.4 Hz, 1H), 2.91 (t, J = 8.7 Hz, 1H), 3.20−3.43 (d, m, J = 14.4 Hz, 3H), 3.81 (s, 3H), 3.93−4.45 (m, 2H), 6.86−6.92, 7.18−7.26, 7.28−7.36, 7.42−7.54 (4m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 25.6, 27.0, 32.3, 52.8, 56.1, 55.4, 58.4, 69.1, 69.6, 113.9, 126.7, 128.3, 128.4, 128.5, 135.7, 140.8, 158.7; MS (EI) m/z 426 (M^+, 0.3), 343 (10), 336 (18), 335 (74), 252 (35), 222 (23), 204 (13), 203 (91), 202 (100), 134 (10), 121 (47), 91 (75); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{29}H_{35}N_2O$ 427.2749, found 427.2763.

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Methyl 4-[(1R,3R*,8aR*)-1-(dibenzylamino)octahydroindolizin-3-yl)]benzoate (**5k**):* white solid (216 mg, 95%); R_f 0.60 (hexane/EtOAc, 8:2); mp 144.5−147.6; IR (neat) ν 3058, 2945, 2792, 1719, 1274, 1110, 1097, 769, 733, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16−1.61 (m, 4H), 1.76−1.95 (m, 4H), 2.04−2.19 (m, 2H), 2.79 (d, J = 10.7 Hz, 1H), 3.06 (t, J = 8.7 Hz, 1H), 3.24 (d, J = 14.4 Hz, 2H), 3.39 (td, J = 8.7, 3.9 Hz, 1H), 3.92 (s, 3H), 4.17 (br s, 2H), 7.23 (t, J = 7.3 Hz, 2H), 7.32 (t, J = 7.5 Hz, 4H), 7.45 (m, 6H), 8.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 25.4, 26.8, 32.1, 52.0, 52.8, 55.8, 58.5, 69.0, 69.6, 126.6, 127.1, 128.2, 128.3, 129.8, 128.7, 140.4, 149.2, 167.1; MS (EI) m/z 454 (M^+, 0.4), 364 (18), 363 (72), 281 (13), 280 (65), 232 (14), 231 (100), 230 (96), 222 (10), 216 (20), 91 (70). Anal. Calcd for $C_{30}H_{34}N_2O_2$: C, 79.26; H, 7.54; N, 6.16. Found: C, 78.80; H, 7.48; N, 6.11.

(1R,3R*,8aR*)-N,N-Dibenzyl-3-[4-(trifluoromethyl)phenyl]-octahydroindolizin-1-amine (**5l**):* beige solid (128 mg, 55%); t_R 19.28; R_f 0.80 (hexane/EtOAc, 7:3); mp 141.6−144.4 °C; IR (neat) ν 3079, 3060, 3030, 2937, 2853, 2792, 2754, 1617, 1322, 1161, 1121, 1102, 1066, 1018, 834, 739, 729, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13−1.64, 1.74−1.99, 2.05−2.22 (3m, 10H), 2.79 (d, J = 10.5 Hz, 1H), 3.06 (t, J = 8.7 Hz, 1H), 3.24 (d, J = 14.4 Hz, 2H), 3.32−3.49 (m, 1H), 3.97−4.42 (m, 2H), 7.20−7.26, 7.29−7.36, 7.43−7.52, 7.58−7.63 (4m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 25.5, 27.0, 32.3, 52.9, 56.0, 58.6, 69.1, 69.7, 124.4 (q, $^1J_{C-F}$ = 271.9 Hz), 125.5 (q, $^3J_{C-F}$ = 3.8 Hz), 126.8, 127.6, 128.4, 128.5, 129.1 (q, $^2J_{C-F}$ = 32.1 Hz), 140.5, 148.0; MS (EI) m/z 464 (M^+, 0.1), 373 (39), 291 (10), 290 (54), 242 (11), 241 (78), 240 (100), 172 (11), 91 (82). Anal. Calcd for $C_{29}H_{31}F_3N_2$: C, 74.98; H, 6.73; N, 6.03. Found: C, 74.95; H, 6.75; N, 5.90.

(1R,3S*,8aR*)-N,N-Dibenzyl-3-decyloctahydroindolizin-1-amine (**5m**):* brown oil (166 mg, 72%); t_R 25.57; R_f 0.83 (hexane/EtOAc, 7:3); IR ν 3079, 3060, 3020, 2922, 2852, 2791, 2754, 1603, 1493, 1452, 1364, 1263, 1148, 1027, 981, 938, 771, 733, 696; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 6.7 Hz, 3H), 1.07−1.45, 1.47−1.89 (2m, 29H), 3.08−3.16, 3.17−3.25 (2m, 2H), 3.29 (d, J = 14.6 Hz, 2H), 3.84−4.29 (m, 2H), 7.17−7.23, 7.26−7.33, 7.39−7.50 (3m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 22.9, 25.1, 25.7, 26.8, 27.0, 28.0, 29.5, 29.8, 29.9, 30.3, 32.1, 32.8, 53.0, 56.1, 58.0, 65.6, 69.8, 126.6, 128.3, 128.4, 140.9; MS (EI) m/z 460 (M^+, 0.4), 370 (20), 369 (71), 238 (18), 237 (100), 236 (50), 166 (12), 138 (12), 124 (42), 122 (18), 111 (17), 110 (51), 98 (11), 97 (21), 96 (13), 91 (72), 84 (12). Anal. Calcd for $C_{32}H_{48}N_2$: C, 83.42; H, 10.50; N, 6.08. Found: C, 83.81; H, 10.23; N, 5.73.

(1R,3R*,8aR*)-N,N-Dibutyl-1-phenyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinolin-3-amine (**5n**):* yellow oil (85 mg, 45%), t_R 21.37; R_f 0.75(hexane/EtOAc, 9:1); IR (neat) ν 3021, 2957, 2921, 2856, 2816, 1598, 1491, 1455, 1320, 1097, 1079, 1029, 803, 751, 703; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 7.2 Hz, 6H; 2 × CH_3), 1.14−1.43 (m, 8H; 4 × CH_2), 1.94 (ddd, J = 14.0, 6.5, 3.6 Hz, 1H; CH), 2.06−2.19 (m, 4H; 2 × CH_2), 2.52−2.65 (m, 3H), 2.92−3.00 (m, 2H), 3.36−3.52 (m, 2H), 4.35 (dd, J = 9.8, 6.5 Hz, 1H; CH), 6.14 (dd, J = 8.1, 0.9 Hz, 1H; ArH), 6.64 (td, J = 7.3, 1.1 Hz, 1H; ArH), 6.79 (td, J = 8.2, 1.7 Hz, 1H; ArH), 7.05 (dd, J = 7.4, 1.2 Hz, 1H; ArH), 7.17−7.29 (m, 5H; ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (2 × CH_3), 20.6, 24.5, 27.9, 30.3, 36.1, 51.8 (9 × CH_2), 60.7, 63.2, 64.2 (3 × CH), 114.9, 117.9, 125.9, 126.3, 128.1, 128.3, 128.7 (9 × ArCH), 125.6, 144.0, 146.9 (3 × ArC); MS (EI) m/z 376 (M^+, 18), 329 (9), 247 (11), 246 (12), 245 (20), 244 (30), 221 (55), 220 (100), 202 (20), 155 (11), 154 (72), 117 (25), 115 (12), 91 (11); HRMS (ESI) m/z [M^+] calcd for $C_{26}H_{36}N_2$ 376.2878, found 376.2889.

(1R,3R*,5R*,8aR*)-N,N-Dibenzyl-5-methyl-3-phenyloctahydroindolizin-1-amine (**5o**):* yellow oil (82 mg, 40%), t_R 28.22; R_f 0.83 (hexane/EtOAc, 8:2); IR (neat) ν 3027, 2926, 2849, 2797, 1492, 1452, 1140, 993, 732, 697, 617; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.54 (d, J = 6.4 Hz, 3H), 1.18−1.44 (m, 5H), 1.72−1.95 (m, 5H), 2.14−2.25 (m, 2H), 3.21 (d, J = 14.2 Hz, 2H; CH_2), 3.23 (t, J = 4.4 Hz, 1H), 3.28 (ddd, J = 9.5, 7.9, 3.6 Hz, 1H), 4.23 (d, J = 14.2 Hz, 2H; CH_2), 7.18−7.25 (m, 3H; 3 × ArH), 7.29−7.34 (m, J = 7.5 Hz, 8H; 8 × ArH), 7.46 (d, J = 7.5 Hz, 4H; 4 × ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3 (CH_3), 25.3, 27.3, 34.2, 35.6 (4 × CH_2), 55.9 (2 × CH_2N), 58.5, 62.9, 69.8, 70.8 (4 × CH), 126.2, 126.6, 126.7, 128.1, 128.4 (15 × ArCH), 140.1, 148.0 (3 × ArC); MS (EI) m/z 319 (73), 222 (49), 207 (20), 187 (64), 186 (89), 117 (14), 106 (10), 104 (12), 92 (11), 91 (100); HRMS (ESI) m/z [M^+] calcd for $C_{29}H_{34}N_2$ 410.2722, [M − Bn]$^+$ 319.2174, found 319.2195.

General Procedure for the Hydrogenolysis of Indolizines 5 to Monobenzylated Indolizidines 6. The indolizine **5** (0.3 mmol) was poured into the hydrogenation flask followed by the addition of Pt (5 wt %)/C (117 mg, 10 mol %) or PtO_2 (11.4 mg, 10 mol %) and glacial HOAc (3 mL), with this mixture being subjected to hydrogenation at ca. 1 atm (balloon) and ambient temperature. The reaction was monitored by TLC and/or GLC until total or steady conversion of the starting material (see Table 3). The catalyst was separated by filtration, and the glacial HOAc was neutralized with 2 M NaOH followed by extraction with EtOAc, drying of the organic phase with Na_2SO_4, and solvent evaporation under vacuum. Purification of the reaction crude by preparative TLC (silica gel, hexane/EtOAc 6:4) afforded the pure indolizidines **6** as single diastereoisomers.

(1R,3R*,8aR*)-N-Benzyl-3-phenyloctahydroindolizin-1-amine (**6h**):* brown oil (63 mg, 68%); t_R 15.38; R_f 0.44 (hexane/EtOAc, 3:7); IR (neat) ν 3029, 2935, 2851, 2789, 1603, 1492, 1451, 1145, 1117, 754, 731, 609; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15−1.31 (m, 1H), 1.38−1.86 (m, 8H), 2.06−2.15 (m, 1H), 2.43 (dt, J = 13.5, 8.0 Hz, 1H), 2.83, (d, J = 10.7 Hz, 1H), 3.07 (t, J = 8.4 Hz, 1H), 3.14 (ddd, J = 7.9, 6.1, 3.1 Hz, 1H), 3.68, 3.86 (AB system, J = 13.4 Hz, 2H), 7.20−7.37 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 25.4, 26.4, 41.7, 51.4, 52.1, 57.5, 68.8, 69.9, 126.8, 126.9, 127.6, 128.1, 128.3, 140.7, 143.3; MS (70 eV) m/z 306 (M^+, 3), 223 (20), 197 (21), 196 (20), 173 (61), 172 (100), 168 (11), 132 (29), 91 (25); HRMS (EI) m/z calcd for $C_{21}H_{26}N_2$ 306.2096, found 306.2092.

(1R,3R*,8aR*)-N-Benzyl-3-(4-methoxyphenyl)octahydroindolizin-1-amine (**6j**):* brown oil; (73 mg, 72%); t_R 18.52; R_f 0.13 (hexane/EtOAc, 6:4); IR (neat) ν 3060, 2951, 2851, 1509, 1426, 1301, 1259, 1112, 896, 734, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19−1.92 (m, 9H), 2.02−2.13 (m, 1H), 2.41 (dt, J = 13.5, 8.0 Hz, 1H), 2.81 (d, J = 10.7 Hz, 1H), 3.02 (t, J = 8.4 Hz, 1H), 3.14 (ddd, J = 7.8, 6.1, 3.1 Hz, 1H), 3.69, 3.87 (AB system, J = 13.4 Hz, 2H), 3.80 (s, 3H), 6.86 (d, J = 8.4 Hz, 2H), 7.21−7.36 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3, 25.3, 26.3, 41.6, 51.4, 52.0, 55.2, 57.4, 68.8, 69.4, 113.7, 126.8, 128.1, 128.3, 128.7, 135.0, 140.6, 158.6; MS (70 eV) m/z 336 (M^+, 2), 253 (21), 252 (10), 231 (10), 227 (39), 226 (13), 212 (17), 207 (13), 203 (58), 202 (100), 162 (34), 135 (12), 134 (20), 132 (39), 106 (16), 92 (10), 91 (66), 84 (12), 77 (14), 65 (10); HRMS (EI) m/z calcd for $C_{22}H_{28}N_2O$ 336.2202, found 336.2185.

(1R,3R*,8aR*)-N-Benzyl-3-[4-(trifluoromethyl)phenyl]octahydroindolizin-1-amine (**6l**):* brown oil (73 mg, 65%); t_R 15.06; R_f 0.48 (hexane/EtOAc, 6:4); IR (neat) ν 3029, 2934, 2852, 2789, 2753, 1509, 1325, 1162, 1119, 1018, 837, 731, 697; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08−1.99 (m, 9H), 2.07−2.29 (m, 1H), 2.34−2.61 (m, 1H), 2.80 (d, J = 10.7 Hz, 1H), 3.08−3.21 (m, 2H), 3.67, 3.84 (AB system, J = 13.3 Hz, 2H), 7.20−7.35 (m, 5H), 7.47, 7.56 (AA′BB′system, J = 8.2 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.2, 25.3, 26.4, 41.8, 51.5, 52.1, 57.7, 68.7, 69.3, 124.3 (q, J = 271.8 Hz) 125.3 (q, J = 3.7 Hz), 126.8, 127.8, 128.1, 128.3, 129.1 (q, J = 32.2 Hz) 140.7, 147.9; MS (70 eV) m/z 374 (M^+, 2), 291 (8), 269 (11), 242 (10), 241 (62), 240 (100), 172 (11), 132 (20), 91 (38), 84 (27); HRMS (EI) m/z calcd for $C_{22}H_{25}F_3N_2$ 374.1970, found 374.1967.

(1R,3R*,8aR*)-N-Benzyl-3-decyloctahydroindolizin-1-amine (**6m**):* brown oil (90 mg, 81%); t_R 19.19; R_f 0.20 (hexane/EtOAc, 3:7); IR (neat) ν 3029, 2922, 2852, 2817, 1566, 1454, 1145, 980, 743, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.7 Hz, 3H), 1.09−1.40 (m, 20H), 1.43−2.04 (m, 9H), 2.2 (dt, J = 13.1, 7.8 Hz, 1H), 2.96−3.07 (m, 1H), 3.19 (d, J = 10.5 Hz, 1H), 3.65, 3.84 (AB system, J = 13.4 Hz, 2H), 7.17−7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 24.6, 25.2, 26.2, 26.6, 29.3, 29.6, 30.0, 31.9, 38.0, 51.6, 52.2, 56.9, 65.3, 69.4, 126.6, 128.1, 128.2, 140.7; MS (70 eV) m/z 370 (M^+, 3), 261 (9), 238 (13), 237 (49), 236 (23), 229 (28), 135 (14), 134 (100), 132 (12), 124 (27), 111 (10), 110 (27), 97 (11), 91 (25); HRMS (EI) m/z Calcd for $C_{25}H_{42}N_2$ 370.3348, found 370.3337.

General Procedure for the Hydrogenolysis of Indolizines 5 to Debenzylated Indolizidines 7. The indolizine **5** (0.3 mmol) was poured into the hydrogenation flask followed by the addition of Pd (20

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wt %)/C (16 mg, 10 mol %) and glacial HOAc (3 mL), with this mixture being subjected to hydrogenation at ca. 1 atm (balloon) and ambient temperature. The reaction was monitored by TLC and/or GLC until total or steady conversion of the starting material (see Table 3). The catalyst was separated by filtration, and the glacial HOAc was neutralized with 2 M NaOH, followed by extraction with EtOAc, drying of the organic phase with Na_2SO_4, and solvent evaporation under vacuum. Compounds **7j** and **7m** did not require any further purification; compounds **7h** and **7l** were purified by preparative TLC (EtOAc). In all cases, the pure indolizidines **7** were obtained as single diastereoisomers.

(1R,3R*,8aR*)-3-Phenyloctahydroindolizin-1-amine (**7h**):* yellow oil (55 mg, 85%); t_R 11.11; R_f 0.20 (EtOAc/MeOH, 8:2); IR (neat) ν 3038, 2932, 2854, 1555, 1455, 1388, 1311, 1145, 754, 698; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21−1.62 (m, 6H), 1.63−1.88 (m, 3H), 2.02 (ddd, J = 7.5, 5.4, 2.7 Hz, 2H), 2.62 (ddd, J = 14.0, 8.8, 8.0 Hz, 1H), 2.83 (d, J = 10.8 Hz, 1H), 3.07 (t, J = 8.4 Hz, 1H), 3.27 (ddd, J = 7.7, 5.1, 2.4 Hz, 1H), 7.15−7.26 (m, 1H), 7.28−7.36 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 25.2, 26.0, 43.9, 51.7, 52.3, 68.6, 69.4, 126.8, 127.4, 128.2, 143.2; MS (70 eV) m/z 217 (M^++1, 1), 216 (M^+, 8), 173 (51), 172 (100), 132 (8), 104 (7), 84 (15); HRMS (EI) m/z calcd for $C_{14}H_{20}N_2$ 216.1626, $C_{14}H_{17}N$ [$M^+ - NH_3$] 199.1361, found 199.1356.

(1R,3R*,8aR*)-3-(4-Methoxyphenyl)octahydroindolizin-1-amine (**7j**):* brown oil (57 mg, 77%); t_R 12.59; R_f 0.17 (acetone); IR (neat) ν 2933, 2851, 1583, 1242, 1035, 828, 626; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95−2.01 (m, 9H), 2.57 (dt, J = 13.9, 8.4 Hz, 1H), 2.73 (s, 2H), 2.8 (d, J = 10.8 Hz, 1H), 2.99 (t, J = 8.4 Hz, 1H), 3.27 (ddd, J = 7.9, 5.2, 2.5 Hz, 1H), 3.78 (s, 3H), 6.85, 7.24 (AA′XX′, J = 8.7 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 25.2, 25.9, 43.7, 51.6, 52.1, 55.1, 68.6, 69.0, 113.6, 128.5, 134.9, 158.5; MS (70 eV) m/z 247 (M^++1, 3), 246 (M^+, 17), 203 (48), 202 (100), 162 (11), 134 (16), 132 (11), 84 (43); HRMS (EI) m/z calcd for $C_{15}H_{22}N_2O$ 246.1732, found 246.1723.

(1R,3R*,8aR*)-3-[4-(Trifluoromethyl)phenyl]octahydroindolizin-1-amine (**7l**):* yellow oil (63 mg, 74%); t_R 10.99; R_f 0.45 (EtOAc/MeOH, 8:2); IR (neat) ν 3024, 2939, 2851, 1553, 1457, 1322, 1162, 1117, 1066, 838; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29−1.60 (m, 4H), 1.73−1.89 (m, 3H), 2.12 (ddd, J = 10.9, 4.9, 2.4 Hz, 1H), 2.60−2.83 (m, 5H), 3.19 (t, J = 8.5 Hz, 1H), 3.37−3.42 (m, 1H), 7.46, 7.57 (AA′XX′ system, J = 8.2 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 25.2, 26.0, 44.2, 51.7, 52.5, 68.7, 68.9, 124.2 (q, J = 272.0 Hz), 125.3 (q, J = 3.6 Hz), 127.6, 129.0 (q, J = 32.0 Hz), 147.8; MS (70 eV) m/z 285 (M^++1, 1), 284 (M^+, 5), 265 (7), 242 (8), 241 (62), 240 (100), 200 (6), 172 (9), 84 (12); HRMS (EI) m/z calcd for $C_{15}H_{19}F_3N_2$ 284.1500, $C_{15}H_{16}F_3N$ [$M^+ - NH_3$] 267.1235, found 267.1221.

(1R,3R*,8aR*)-3-Decyloctahydroindolizin-1-amine (**7m**):* brown oil (77 mg, 92%); t_R 15.44; R_f 0.20 (EtOAc/MeOH, 7:3); IR (neat) ν 2921, 2851, 1560, 1467, 1458, 1387, 1147, 1121, 811, 721, 687; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 6.7 Hz, 3H), 1.06 (ddd, J = 13.6, 8.1, 2.7 Hz, 1H), 1.20−1.85 (m, 27H), 2.04−2.19 (m, 2H), 2.35 (dt, J = 13.6, 8.3 Hz, 1H), 3.12−3.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 24.2, 25.2, 25.9, 26.4, 29.3, 29.6, 29.9, 31.9, 33.5, 40.2, 52.1, 51.8, 65.0, 69.5; MS (70 eV) m/z 280 (M^++1, 1), 279 (M^+, 1), 237 (16), 236 (11), 140 (10), 139 (100), 124 (17), 122 (15), 110 (25), 96 (11). Anal. Calcd for $C_{18}H_{36}N_2$: C, 77.08; H, 12.94; N, 9.99. Found: C, 76.72; H, 12.65; N, 9.50.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01782.

^{1}H, ^{13}C and 2D NMR spectra, and selected X-ray data (PDF)

X-ray data for compound **5a** (CIF)

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Notes

The authors declare no competing financial interest.

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