JOC The Journal of Organic Chemistry

Article

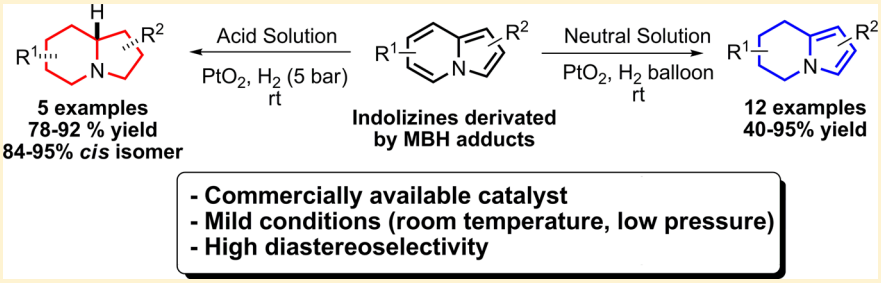
pubs.acs.org/joc

Selective Hydrogenation of Indolizines: An Expeditious Approach To Derive Tetrahydroindolizines and Indolizidines from Morita–Baylis–Hillman Adducts

Bruno V. M. Teodoro, José Tiago M. Correia, and Fernando Coelho*

Laboratory of Synthesis of Natural Products and Drugs, Institute of Chemistry, University of Campinas, P.O. Box 6154, 13083-970 Campinas, São Paulo, Brazil

Supporting Information



ABSTRACT: In this study, we describe the hydrogenation of indolizines derived from Morita–Baylis–Hillman adducts. We demonstrate that functionalized tetrahydroindolizines and indolizidines can be prepared selectively, at low pressure, by simply adjusting the acidity of the medium. Using this simple and straightforward strategy, substituted tetrahydroindolizines and indolizidines were obtained diastereoselectively in high yield.

INTRODUCTION

Indolizines and tetrahydroindolizines are polyunsaturated N-heterocycles that have caught the attention of the chemical community, because of their broad potential in biological and synthetic applications. Together with the quinolizidine nucleus, it is estimated that these structural moieties are found in approximately 25–30% of known alkaloids.[1] Glycosidase inhibitor activity (e.g., castanospermine and swainsonine alkaloids, Scheme 1)[2] and pheromone activity (e.g., monomorine, Scheme 1)[3] are among the highlighted biological properties of these alkaloids. Some indolizidines are directly related to the occurrence of diseases. For instance, slaframine is an indolizidine that causes slobber disease, which negatively affects the cattle industry.[4] Unlike indolizidines, tetrahydroindolizines are rarely found in alkaloid structures.

Anticancer activity (e.g., rhazinilam and rhazinicine (Scheme 1)[5] and antimicrobial activity (e.g., polygonatine A, polygonatine B, and kinganone (Scheme 1)[6]) are among the biological activities shown by this class of compounds. Alkaloids isolated from *Myrmicaria* ants (Myrmicarines 217, 215A, and 215B) are interesting examples, because their biological profiles remain poorly understood.[7] Although several methodologies have been described, these molecules represent a challenge from a synthetic point of view, because of their low stability in air, silica gel, and alumina.

Many reports focused on the preparation of indolizines[8] and tetrahydroindolizines[9] can be found in the literature, with each focusing on specific substitution patterns.

The synthetic and biological relevance of these molecules justify the interest in the development and/or improvement of the synthetic methodologies used to prepare them. The rationalization that tetrahydroindolizines and indolizidines could be obtained by the partial and full hydrogenation of indolizines, respectively, is reasonable (Scheme 2).

Many methods for the preparation of indolizines are available in the literature.[10] Furthermore, indolizines can be easily accessed, in a few steps, by the intramolecular cyclization of Morita–Baylis–Hillman (MBH) adducts prepared from suitable acrylates or α,β-unsaturated ketones and adequately substituted 2-pyridinecarboxaldehydes.

Among the strategies based on MBH adducts we have mentioned, acetylation followed by heating,[11] allylic bromination,[12] and direct heating of the MBH adduct under MW conditions afford indolizines.[13]

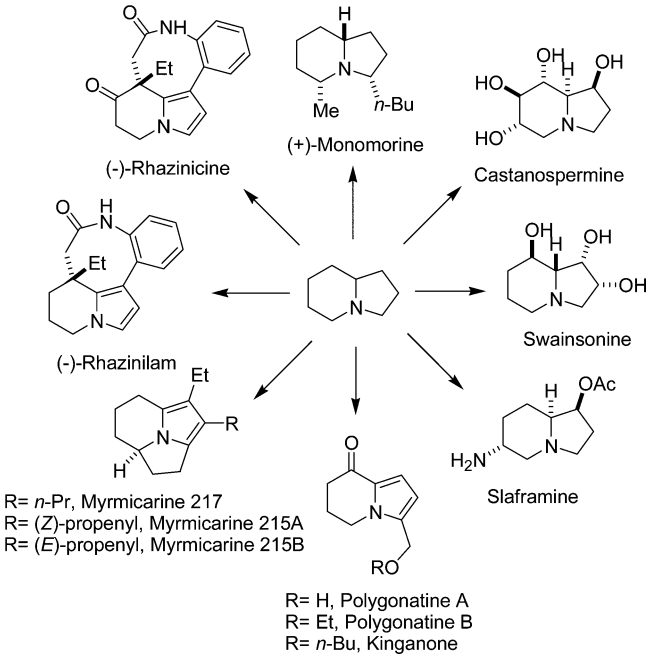
Additionally, a recent report by Basavaiah described a one-step autocatalytic methodology for preparing indolizines using pyridine-2-carboxyaldehydes or 2-acetopyridines and vinyl ketones, promoted by TMSOTf.[14] Curiously, an in situ cyclization is observed during the preparation of the MBH adduct from 2-cyclohexenone.[12] Although this cyclization occurs without substrate preactivation, it can be accelerated in the presence of silica gel.

Despite the great number of methodologies used to access tetrahydroindolizines and indolizidines,[9] few of them have

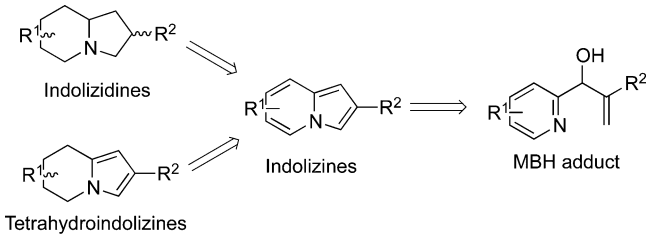
Received: October 28, 2014
Published: January 30, 2015

DOI: 10.1021/jo502471q
J. Org. Chem. 2015, 80, 2529–2538

Scheme 1. Examples of Indolizidinic and Tetrahydroindolizinic Alkaloids



Scheme 2. Retrosynthetic Analysis for the Preparation of Indolizidines and Tetrahydroindolizines



focused on the preparation of these heterocycles via partial and full hydrogenation, respectively (Scheme 2). Most data related to this approach have been described in the patent literature.[15] However, high temperatures and pressures are required and the substitution patterns are limited. For example, Soldatenkov reported a partial hydrogenation to obtain a unique tetrahydroindolizine using Re_2S_7 at 260 °C and 140 atm.[16] Recently, the first asymmetric partial hydrogenation of indolizines was reported by the Glorius group. In this case, a NHC-Ru chiral complex was used as the catalyst.[17] Although high yields and high selectivity were achieved, the scope (i.e., substitution pattern of indolizines) was relatively limited, showing that much remains to be done in this area.

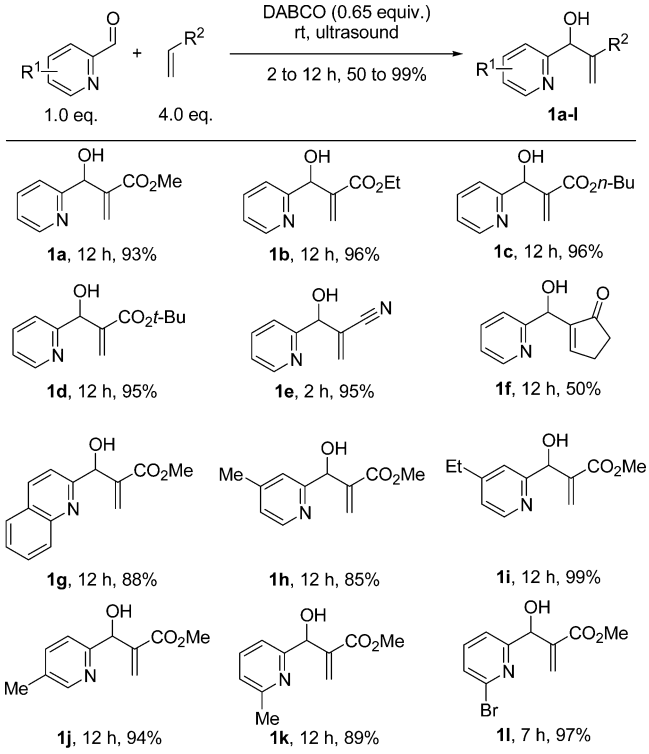
The complete hydrogenation of indolizines presents several challenges regarding the aspects of enantio- and diastereoselectivity. The first study of this type of transformation was reported by Poponova, in which 10 examples of indolizidines were prepared in moderate yields and poor diastereoselectivity (1:1.4) in favor of the cis diastereoisomer.[18] Recently, Gevorgyan reported a unique example using Adams's catalyst. In this case, a strong acid (HBr) and a hydrogenation pressure of 5 atm were used to afford (±)-monomorine with moderate diastereoselectivity.[19] With the aim of demonstrating the applicability of indolizines prepared via a multicomponent reaction catalyzed by a copper nanoparticle, Alonso and Yus also reported a unique example of the full hydrogenation of indolizines. In this case, the reaction gave the desired indolizidine with high diastereoselectivity using Adams catalyst under a pressure of 55 psi with acetic acid as the solvent.[20]

Driven by the previous data provided in the literature and with the intent of expanding our understanding of the behavior of indolizines, we explored herein the catalytic heterogeneous hydrogenation of indolizines derived from Morita–Baylis–Hillman adducts to obtain both 5,6,7,8-tetrahydroindolizines and indolizidines.

RESULTS AND DISCUSSION

Preparation of Morita-Baylis-Hillman (MBH) adducts and indolizines. Morita–Baylis–Hillman (MBH) adducts were prepared using a methodology created by our group,[21,22] whereby they were obtained in good to excellent yields (Table 1).

Table 1. Preparation of MBH Adducts

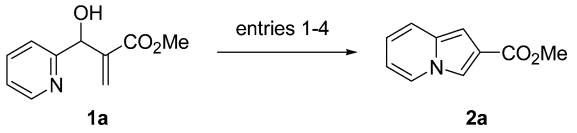


Once the MBH adducts were synthesized, the next step was the optimization of the methodology used to prepare the indolizines. Among the methods available in the literature, we chose acetylation followed by thermal treatment and allylic bromination to get the desired indolizines.

When the allylic bromination using PBr_3 was tested, the indolizine was obtained in very low yield (entry 1, Table 2). Using the milder Appel reaction conditions,[23] the yield increased to 20% (entry 2, Table 2). A similar result was obtained when the methodology described by Bode was used (entry 3, Table 2). Modifications of the acetylation conditions and thermal cyclization (entry 4, Table 2) led to a net increase in the overall yield, which improved to 55% for the two steps. Using these better optimization conditions, a set of indolizines

DOI: 10.1021/jo502471q
J. Org. Chem. 2015, 80, 2529–2538

Table 2. Optimization of the Conditions for the Preparation of Indolizines

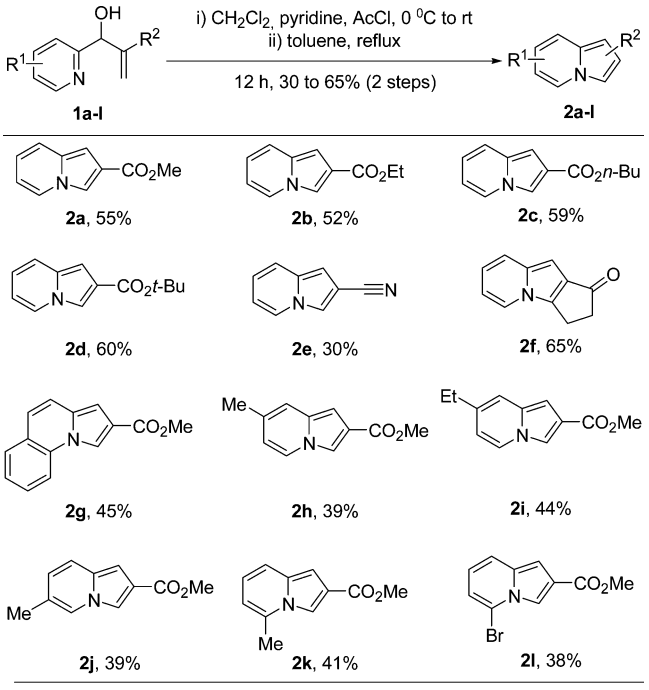


entry	conditions	yield (%)
1	PBr_3, CH_2Cl_2, 0 °C	7
2	PPh_3, CBr_4, CH_2Cl_2, 0 °C to room temp	20
3	(i) Ac_2O, 100 °C; (ii) 130 °C	20[a]
4	(i) Py, AcCl, CH_2Cl_2, 0 °C to room temp, 30 min; (ii) toluene, reflux 12 h	55[a]

[a]Overall yield for two steps.

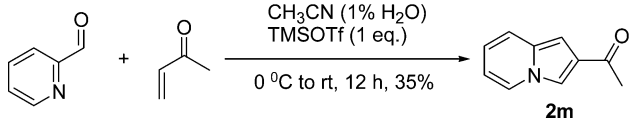
was prepared from MBH adducts. Good overall yields derived from acrylates and cyclopentenone could be obtained, with a yield of up to 65% for two steps (Table 3).

Table 3. Preparation of Indolizines

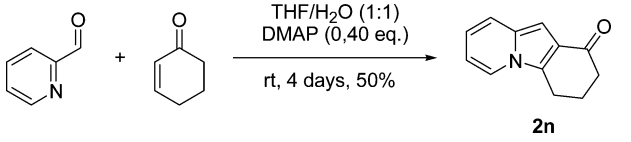


Additionally, indolizines derived from methyl vinyl ketone (MVK) and cyclohexenone were also prepared. Indolizine **2m** was obtained by the treatment of 2-pyridinecarboxaldehyde with TMSOTf in the presence of MVK in acetonitrile containing 1% water (Scheme 3). Indolizine **2n** was prepared via the reaction between 2-pyridinecarboxaldehyde and 2-cyclohexenone in the presence of DMAP as the catalyst (Scheme 4). Both methodologies were reproduced from the

Scheme 3. Preparation of Indolizine 2m



Scheme 4. Preparation of Indolizine 2n

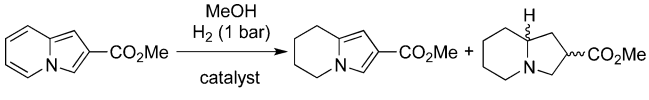


literature, and yields and purities were in accordance with the reported data.

Hydrogenation. Once the indolizines were prepared, the performance of the hydrogenation reactions was evaluated by screening different catalysts. Indolizine **2a** was chosen as a model to optimize the reaction conditions. The following catalysts were tested: Pd/C, PtO_2, Rh/Al_2O_3, and Rh/C.

Notably, no reaction was observed when rhodium catalysts (i.e., Rh/Al_2O_3 and Rh/C) were used. Indeed, the starting material was recovered in both cases after 24 h. In contrast, partial hydrogenation was observed when Pd/C and PtO_2 were used as the catalysts, affording 5,6,7,8-tetrahydroindolizine (**3a**) in 90% and 93% yields, respectively. The reaction in the presence of PtO_2 was faster than the reaction in the presence of Pd/C. No indolizidine was detected in the reaction medium, even when the pressure was increased (entries 1−5, Table 4).

Table 4. Optimization of the Conditions for the Preparation of Tetrahydroindolizines and Indolizidines



entry	catalyst	additive	time (h)	yield (%)	3a:4a
1	Rh/Al_2O_3		12		
2	Rh/C		12		
3	Pd/C		4	90	100:0
4	PtO_2		2	93	100:0
5	PtO_2		4	92	100:0
6	PtO_2	AcOH (1 equiv)	4	91	99:1
7	PtO_2	TFA (1 equiv)	4	78	0:100

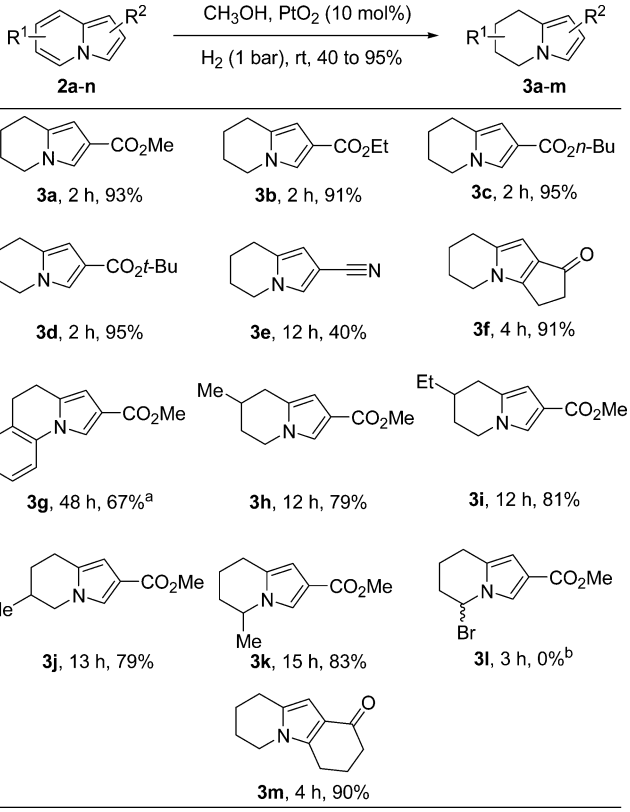
Additional reactions were performed that examined the effect of acids as additives. In these cases, the same conditions were maintained. When the reaction was performed in the presence of acetic acid, a tiny amount of the corresponding indolizidine was observed by TLC. However, tetrahydroindolizine was still obtained as the major product (91% yield). Full hydrogenation was achieved only when the reaction was performed using TFA as the additive. Under this condition, only the desired indolizidine was detected by TLC at the end of the reaction. After isolation, indolizidine **4a** was obtained in 78% yield (entries 6 and 7, Table 4).

After the procedure had been optimized, the partial hydrogenation was performed (Table 5). The results showed that indolizines without substituents on six-membered rings gave their corresponding tetrahydroindolizines in yields varying from 65% to 95%, with short reaction times (up to 4 h, entries 1−4, 6, 12, and 13). The presence of a cyano group led to a drastic drop in the yield (compound **3e**, Table 5). Notably, reduction of the cyano group was not detected.

This result is likely associated with the fact that this functional group competes with the aromatic system under

DOI: 10.1021/jo502471q
J. Org. Chem. 2015, 80, 2529−2538

Table 5. Synthesis of Tetrahydroindolizines by Partial Hydrogenation of Indolizines



[a]Reaction was performed with 5 bar pressure of H_2. [b]**3a** was recovered as the unique product in 65% yield.

hydrogenation conditions. Indolizines containing substituents on the six-membered ring afforded tetrahydroindolizines in yields varying from 67% to 83% with longer reaction times (up to 48 h). This behavior is likely caused by the increased steric hindrance incurred as a result of these substituents, which could compromise the adsorption of the substrate on the catalyst surface. In particular, a slight increase in pressure to 4 bar was necessary for analogue **2g** to synthesize tetrahydroindolizine **3g** (Table 5).

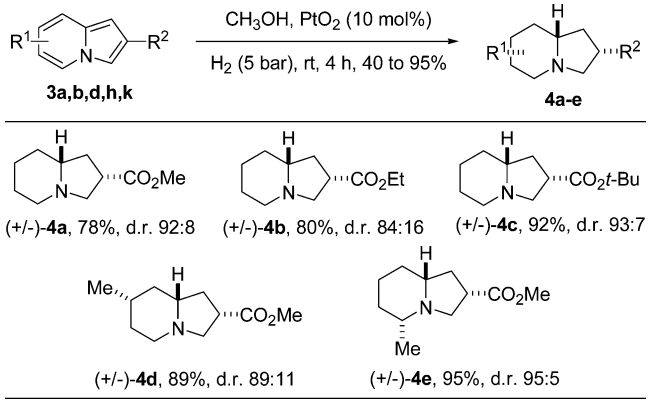
It is noteworthy that Gevorgyan reported the unique example of hydrogenation of this same substrate some years ago, using the Birch reaction.[24] However, this methodology failed when it was tested with indolizines structurally similar to those obtained from Morita−Baylis−Hillman adducts, leading to the decomposition of the starting materials.[24] These data show that the methodology described in this study is mild and easy to handle.

Product **3a** was obtained when brominated indolizine **2l** underwent the same partial hydrogenation condition. It is likely that a hydrogenolysis of the C−Br bond occurred to give indolizine **2a**,[25] which then is partially hydrogenated to afford tetrahydroindolizine **3a**.

Full hydrogenation was also investigated, and the results are summarized in Table 6. Indolizidines were obtained in 78−95% yield and 84−95% dr in favor of the cis diastereoisomer. All indolizidines showed the Bohlmann band between 2725 and 2793 cm^{-1},[26] indicating that they adopt a conformation where substituents on the six-membered rings are in the equatorial position.[27]

Diastereoisomeric ratios were obtained by ^1H NMR analysis and uncoupled ^{13}C NMR analysis without NOE.[28] By extension

Table 6. Full Hydrogenation of Indolizines



of ^1H NMR spectra to the region between 2.0 and 3.5 ppm, it was possible to observe the presence of signals with very low intensity, which can possibly be attributed to a minor diastereoisomer. By integrating the ^{13}C NMR without NOE spectra signals, the same ratio was found. In this way, the dr ratio was determined by ^1H NMR analysis followed by confirmation using ^{13}C NMR without NOE analysis (see Figure 86 in the Supporting Information).

To confirm this observation, a GC-MS analysis of (±)-indolizidine **4c** was performed, which detected only two peaks with the same mass spectra. Integration of these peaks showed that same ratio had occurred as that observed in the analysis of the ^{13}C NMR without NOE data (see Figure 112 in the Supporting Information).

Relative configurations of the diastereoisomeric centers 2 and 8a of our indolizidines were determined via the spatial coupling between hydrogens 2, 3α, and 8a observed by NOESY. Hydrogen H3α couples spatially with H2, whereas H3α couples spatially with H8a. From these observations, a cis relative configuration of hydrogens 2 and 8a could be determined. This relative stereochemistry was observed in all indolizines synthesized in this work (Figure 1).

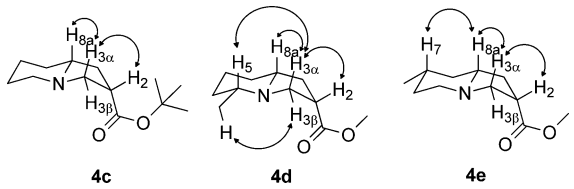


Figure 1. NOESY data of indolizidines **4c−e**.

Relative to indolizidine (±)-**4d**, a spatial coupling between hydrogens H8a and H7 could be observed. Thus, a cis relative configuration among hydrogens 2, 7, and 8a could be assigned. For indolizidine (±)-**4e**, a coupling between H3α and H5 could be detected, whereas H3β couples with the methyl group bonded to carbon 5. Thus, a cis relative configuration among hydrogens 2, 5, and 8a could be assigned.

Some additional experiments were performed in this work to understand the participation of a strong acid such as TFA in the hydrogenation reactions. It is known that indolizines can be protonated on carbons 1 and 3, which is associated with the strength and nature of the acid.[29] Assuming this characteristic, two ^1H NMR analyses of indolizine **2a** were performed under different acidic conditions, with $CDCl_3$ as solvent: one analysis used acetic acid (pK_a 4.76),[30] and the other analysis used TFA

DOI: 10.1021/jo502471q
J. Org. Chem. 2015, 80, 2529−2538

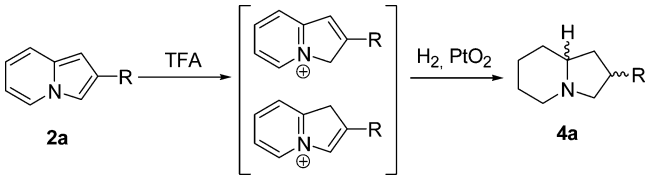
(pK_a 0.23).[30] In accordance with the obtained NMR spectra, no modification of the indolizine structure was observed when it was treated with acetic acid (see Figure 111B in the Supporting Information). However, in addition to a rapid change of the solution's color from colorless to yellowish, a significant modification of the indolidizine structure was observed when it was treated with TFA, as evidenced by comparison with the ^{1}H NMR spectra of indolizine in the absence of this strong acid (see Figure 111C in the Supporting Information).

A drastic alteration of the pattern of the aromatic hydrogens and the appearance of broad bands downfield, which are superimposed with the hydrogens of the pyridinic ring moiety, were also observed (see, Figure 111D in the Supporting Information). These modifications can be rationalized by assuming that the pyrrole portion of indolizine is protonated, as reported in a previous work.[31]

Therefore, another ^{1}H NMR spectrum of **2a** was obtained to confirm this protonation, this time using TFA-d as the solvent. The complete disappearance of hydrogens 1 and 3 was observed because they were exchanged for deuterium atoms. In this spectrum there were only four hydrogen signals in the aromatic region beyond the signal of the methyl ester moiety, which refer to the four hydrogen atoms present on the six-membered ring. In addition, an intensification of the TFA residual signal was observed (see the Supporting Information).

From these NMR data, it can be concluded that TFA is sufficiently strong to protonate carbons 1 and 3 on indolizine and that this cationic intermediate is now susceptible to complete hydrogenation, which can give the desired indolizidines (Scheme 5).

Scheme 5. Proposed Pathways for Hydrogenation



Another experiment used to understand the interesting behavior of these N-heterocycles was an evaluation of the reactivity of these substrates against the hydrogenation catalysts used in this work. Initially, the different behaviors of the catalysts were attributed to electronic factors. To confirm these effects, indolizine **2a** was reduced with $LiAlH_4$ to **2o** (83% yield),[13] which was then subjected to hydrogenation conditions using PtO_2, Pd/C, and Rh/Al_2O_3 in MeOH under hydrogen atmospheric pressure. No reaction was observed when PtO_2 and Pd/C were used as the catalysts, and the starting material was recovered. In contrast, when Rh/Al_2O_3 was used as catalyst, the complete hydrogenated product (±)-**4f** was obtained in 98% yield with a 66.5:33.5 cis:trans ratio (Scheme 6).

The diastereoisomeric ratio was determined by comparing the obtained ^{1}H NMR spectra with known spectra present in the literature.[32]

These experiments led to the conclusion that the reactivity of indolizines with different hydrogenation catalysts is also dependent on the electronic density of indolizine itself, which can be modulated by the rational incorporation of substituents in the indolizine structure.

CONCLUSION

Herein, we have described a simple and direct approach to synthesize 5,6,7,8-tetrahydroindolizines and indolizidines using MBH adducts as building blocks. During its development, it was discovered that partial or full hydrogenation product formation could be modulated by a simple pH adjustment of the reaction media. A special catalyst is not necessary, and the reactions occur under low pressure and at room temperature. Starting from MBH adducts, tetrahydroindolizines with a diverse substitution pattern were obtained in overall yields ranging from 12% to 57%, whereas indolizidines were obtained in overall yields ranging from 35% to 43%, with high diastereoselectivities that range from 84% to 95% in favor of the cis diastereoisomer.

To more fully comprehend the reactivity and electronic characteristics of such indolizines, theoretical calculations are currently underway.

EXPERIMENTAL SECTION

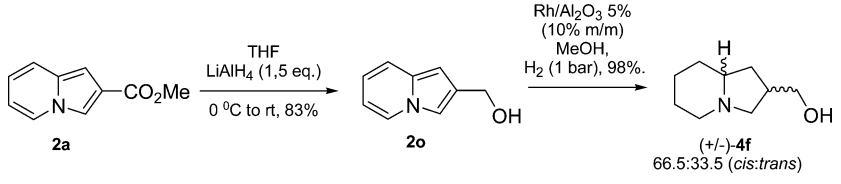
General Protocol for Preparation of MBH Adducts 1a–l. To a mixture of aldehyde (5 mmol) and acrylate or vinyl ketone (4 equiv) was added DABCO (0.65 equiv), and the solution was sonicated in the ultrasound bath for 2–12 h. Afterward, the acrylate was removed and the crude residue was dissolved in ethyl acetate (30 mL). The resulting solution was washed with distilled water (2 × 30 mL) and brine (1 × 30 mL) and dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (silica flash, ethyl acetate 30–100% in hexane) to give the MBH adducts as pure compounds. All adducts are known.

*Methyl 2-[hydroxy(pyridin-2-yl)methyl]prop-2-enoate (**1a**):*[9,33] 0.89 g, 93% yield; yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.69 (s, 3H), 4.84 (sl, 1H), 5.59 (s, 1H), 5.93 (s, 1H), 6.32 (s, 1H), 7.17 (ddd, 1H, J = 0.8 Hz, 4.9 and 7.8 Hz), 7.38 (d, 1H, J = 7.8 Hz), 7.64 (td, 1H, J = 1.7 and 7.8 Hz), 8.50 (d, 1H, J = 4.9 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 52.0, 72.3, 121.5, 122.9, 127.0, 137.0, 141.9, 148.5, 159.7, 166.7 ppm.

*Ethyl 2-[hydroxy(pyridin-2-yl)methyl]prop-2-enoate (**1b**):*[11a,34] 0.99 g, 96% yield; yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.18 (t, 3H, J = 7.1 Hz), 4.13 (q, 2H, J = 7.1 Hz), 4.87 (sl, 1H), 5.25 (s, 1H), 5.58 (s, 1H), 5.90 (s, 1H), 6.31 (s, 1H), 7.15 (ddd, 1H, J = 0.7, 4.8, and 7.7 Hz), 7.37 (d, 1H, J = 7.7 Hz), 7.62 (td, 1H, J = 1.7 and 7.7 Hz), 8.48 (d, 1H, J = 4.8 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 14.2, 60.9, 72.4, 121.4, 122.7, 126.8, 136.9, 142.2, 148.4, 159.8, 166.2 ppm.

*Butyl 2-[hydroxy(pyridin-2-yl)methyl]prop-2-enoate (**1c**):* 1.09 g, 93% yield; yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.83 (t, 3H, J = 7.3 Hz), 1.18–1.32 (m, 2H), 1.46–1.57 (m, 2H), 4.06 (t, 2H, J = 6.6 Hz),

Scheme 6. Full Hydrogenation of Indolizine Mediated by Rhodium, without the Addition of Acid



DOI: 10.1021/jo502471q
J. Org. Chem. 2015, 80, 2529–2538

4.93 (sl, 1H), 5.56 (s, 1H), 5.90 (s, 1H), 6.31 (s, 1H), 7.11−7.17 (m, 1H), 7.36 (d, 1H, J = 7.8 Hz), 7.61 (td, 1H, J = 1.7 and 7.8 Hz), 8.47 (d, 1H, J = 4.2 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 13.8, 19.2, 30.6, 64.8, 72.4, 121.3, 122.7, 126.8, 136.9, 142.1, 148.3, 159.8, 166.3 ppm. HRMS (FT-MS): calcdfor $C_{13}H_{18}NO_3$ $(M + H)^+$ 236.12812, found 236.12814.

tert-Butyl 2-[hydroxy(pyridin-2-yl)methyl]prop-2-enoate (**1d**): 1.11 g, 95% yield; yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.35 (s, 9H), 4.83 (sl, 1H), 5.52 (s, 1H), 5.81 (s, 1H), 6.23 (s, 1H), 7.14 (dd, 1H, J = 4.8 and 7.7 Hz), 7.36 (d, 1H, J = 7.7 Hz), 7.62 (td, 1H, J = 1.7 and 7.7 Hz), 8.48 (d, 1H, J = 4.8 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 28.1, 72.7, 81.4, 121.2, 122.6, 126.2, 136.9, 143.4, 148.3, 160.2, 165.5 ppm. HRMS (FT-MS): calcdfor $C_{13}H_{18}NO_3$ $(M + H)^+$ 236.12812, found 236.12786.

2-[Hydroxy(pyridin-2-yl)methyl]prop-2-enenitrile (**1e**):[11a,21] 0.76 g, 95% yield; pale yellow solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.27 (s, 1H), 6.02 (s, 1H), 6.19 (s, 1H), 7.27 (ddd, 1H, J = 0.6, 4.8, and 7.7 Hz), 7.38 (d, 1H, J = 7.7 Hz), 7.74 (td, 1H, J = 1.6 and 7.7 Hz), 8.54 (d, 1H, J = 4.8 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 73.1, 116.9, 121.4, 123.9, 125.9, 131.2, 137.6, 148.6, 156.3 ppm.

2-[Hydroxy(pyridin-2-yl)methyl]cyclopent-2-en-1-one (**1f**): 0.47 g, 50% yield; yellow solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.39−2.44 (m, 2H), 2.52−2.60 (m, 2H), 4.99 (sl, 1H), 5.56 (s, 1H), 7.15−7.20 (m, 1H), 7.46−7.54 (m, 2H), 7.61−7.67 (m, 1H), 8.49 (d, 1H, J = 4.4 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 26.9, 35.5, 68.5, 121.5, 123.0, 137.2, 147.8, 148.3, 159.3, 160.2, 209.0 ppm. HRMS (FT-MS): calcdfor $C_{11}H_{12}NO_2$ $(M + H)^+$ 190.08626, found 190.08615.

Methyl 2-[hydroxy(quinolin-2-yl)methyl]prop-2-enoate (**1g**):[11a,35] 1.07 g, 88% yield; red oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.71 (s, 3H), 5.25 (s, 1H), 5.77 (s, 1H), 5.97 (s, 1H), 6.37 (s, 1H), 7.43 (d, 1H, J = 8.4 Hz), 7.47−7.53 (m, 1H), 7.65−7.72 (m, 1H), 7.77 (dd, 1H, J = 0.8 and 8.4 Hz), 8.07 (t, 2H, J = 8.4 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 52.1, 72.0, 119.0, 126.7, 127.7, 129.0, 130.0, 137.2, 141.9, 146.5, 159.5, 166.8 ppm.

Methyl 2-[hydroxy(4-methylpyridin-2-yl)methyl]prop-2-enoate (**1h**): 0.88 g, 85% yield; white solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.32 (s, 3H), 3.71 (s, 3H), 4.84 (sl, 1H), 5.54 (s, 1H), 5.92 (s, 1H), 6.32 (s, 1H), 6.99 (d, 1H, J = 5.1 Hz), 7.18 (s, 1H), 8.35 (d, 1H, J = 5.1 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 21.3, 52.1, 72.2, 122.1, 123.9, 127.0, 142.1, 148.1, 148.3, 159.5, 166.8 ppm. HRMS (FT-MS): calcdfor $C_{11}H_{14}NO_3$ $(M + H)^+$ 208.09682, found 208.09657.

Methyl 2-[hydroxy(4-ethylpyridin-2-yl)methyl]prop-2-enoate (**1i**): 1.09 g, 99% yield; colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.21 (t, 3H, J = 7.6 Hz), 2.62 (q, 2H, J = 7.6 Hz). 3.71 (s, 3H), 4.81 (sl, 1H), 5.56 (s, 1H), 5.91 (s, 1H), 6.32 (s, 1H), 7.00−7.03 (m, 1H), 7.21 (s, 1H), 8.38 (d, 1H, J = 5.0 Hz) ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 14.4, 28.4, 51.9, 72.2, 120.9, 122.5, 126.8, 142.1, 148.2, 154.2, 159.6, 166.7 ppm. HRMS (FT-MS): calcdfor $C_{12}H_{16}NO_3$ $(M + H)^+$ 222.11247, found 222.11241.

Methyl 2-[hydroxy(5-methylpyridin-2-yl)methyl]prop-2-enoate (**1j**): 0.97 g, 94% yield; colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.30 (s, 3H), 3.71 (s, 3H), 4.72 (d, 1H, J = 6.4 Hz), 5.56 (d, 1H, J = 6.4 Hz), 5.92 (s, 1H), 6.31 (s, 1H), 7.26−7.29 (m, 1H), 7.45 (dd, 1H, J = 1.5 and 8.0 Hz), 8.34 (s, 1H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 18.2, 52.0, 72.1, 120.9, 126.7, 132.3, 137.6, 142.1, 148.7, 156.8, 166.8 ppm. HRMS (FT-MS): calcdfor $C_{11}H_{14}NO_3$ $(M + H)^+$ 208.09682, found 208.09673.

Methyl 2-[hydroxy(6-methylpyridin-2-yl)methyl]prop-2-enoate (**1k**):[11a] 0.92 g, 89% yield; colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.53 (s, 3H), 3.72 (s, 3H), 5.16 (sl, 1H), 5.57 (s, 1H), 5.91 (s, 1H), 6.30 (s, 1H), 7.03 (d, 1H, J = 7.6 Hz), 7.13 (d, 1H, J = 7.6 Hz), 7.52 (t, 1H, J = 7.6 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 24.3, 52.0, 71.4, 118.2, 122.3, 126.7, 137.2, 142.3, 157.2, 158.5, 166.8 ppm.

Methyl 2-[(6-bromopyridin-2-yl)(hydroxy)methyl]prop-2-enoate (**1l**): 1.32 g, 97% yield; colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.73 (s, 3H), 4.20 (d, 1H, J = 7.0 Hz), 5.56 (d, 1H, J = 7.0 Hz), 5.94 (s, 1H), 6.36 (s, 1H), 7.36−7.41 (m, 1H), 7.49−7.55 (m, 1H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 52.2, 72.4, 120.3, 127.2, 127.6, 139.3, 141.0, 141.2, 161.5, 166.6 ppm. HRMS (FT-MS): calcdfor $C_{10}H_{11}BrNO_3$ $(M + H)^+$ 271.99168 (^{79}Br), 273.98963 (^{81}Br), found 271.9922 (^{79}Br), 273.9902 (^{81}Br).

General Protocol for Preparation of Indolizines 2a−l. To a mixture of adducts **1a−l** (3 mmol) and pyridine (1.5 equiv) in anhydrous CH_2Cl_2 (5 mL) under a nitrogen atmosphere at 0 °C was added, dropwise, acetyl chloride (1.5 equiv). The resulting mixture was stirred for 10 min at 0 °C. Then, the reaction mixture was warmed to room temperature and stirred for 1 h more. After that, a saturated solution of $NaHCO_3$ (10 mL) was carefully added and the biphasic solution was stirred vigorously for 30 min. Then, the organic layer was separated and the aqueous phase was extracted twice with CH_2Cl_2 (10 mL each time). The organic phases were combined, washed with brine (1 × 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was refluxed in toluene (10 mL) for 12 h. Then, the solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica flash, ethyl acetate 10−40% in hexane) to furnish the corresponding indolizines.

Methyl indolizine-2-carboxylate (**2a**): 0.29 g, 55% yield; white solid. mp 101−102 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.86 (s, 3H), 6.49 (td, 1H, J = 1.1 and 7.1 Hz), 6.65 (ddd, 1H, J = 1.1, 6.5, and 9.1 Hz), 6.79 (s, 1H), 7.32 (d, 1H, J = 9.1 Hz), 7.76 (d, 1H, J = 1.0 Hz), 7.82 (dd, 1H, J = 1.0 and 7.1 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 51.6, 100.6, 112.4, 116.0, 118.3, 119.8, 120.4, 125.5, 132.9, 165.7. IR (KBr): ν 1713, 1634, 1571, 1541, 1849, 1216 cm^{-1}. HRMS (FT-MS): calcdfor $C_{10}H_{10}NO_2$ $(M + H)^+$ 176.07061, found 176.07041.

Ethyl indolizine-2-carboxylate (**2b**): 0.29 g, 52% yield; gray solid, mp 63−64 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.34 (t, 3H, J = 7.1 Hz), 4.32 (q, 2H, J = 7.1 Hz), 6.44 (t, 1H, J = 6.7 Hz), 6.60 (dd, 1H, J = 6.7 and 9.1 Hz), 6.79 (s, 1H), 7.29 (d, 1H, J = 9.1 Hz), 7.75−7.79 (m, 2H) ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 14.5, 60.2, 100.5, 112.2, 115.9, 115.9, 118.1, 120.1, 120.3, 125.4, 132.8, 165.2. IR (KBr): ν 3123, 3062, 2996, 2979, 1694, 1544, 1519, 1500, 1350, 1304, 1252 cm^{-1}. HRMS (FT-MS): calcdfor $C_{11}H_{12}NO_2$ $(M + H)^+$ 190.08626, found 190.08620.

Butyl indolizine-2-carboxylate (**2c**): 0.38 g, 59% yield, yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.96 (t, 3H, J = 7.3 Hz) 1.38−1.53 (m, 2H), 1.69−1.77 (m, 2H), 4.27 (t, 3H, J = 6.6 Hz), 6.47 (td, 1H, J = 1.1 and 7.1 Hz), 6.63 (ddd, 1H, J = 0.9, 7.3, and 9.8 Hz), 6.81 (s, 1H), 7.31 (d, 1H, J = 9.1 Hz), 7.76 (d, 1H, J = 0.8 Hz), 7.81 (dd, 1H, J = 0.9 and 7.1 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 13.9, 19.4, 31.0, 64.2, 100.5, 112.3, 115.9, 118.2, 120.2, 120.4, 125.5, 132.9, 165.4 ppm. IR (film): ν 3133, 2959, 2872, 1709, 1636, 1544, 1518, 1498, 1458, 1410, 1358, 1304 cm^{-1}. HRMS (FT-MS): calcdfor $C_{13}H_{16}NO_2$ $(M + H)^+$ 218.11756, found 218.11781.

tert-Butyl indolizine-2-carboxylate (**2d**): 0.39 g, 60% yield; yellow solid, mp 42−43 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.57 (s, 9H), 6.48 (td, 1H, J = 1.2 and 7.0 Hz), 6.63 (ddd, 1H, J = 1.0, 6.5, and 9.0 Hz), 6.75 (s, 1H), 7.31 (d, 1H, J = 9.0 Hz), 7.70 (d, 1H, J = 1.2 Hz), 7.82 (dd, 1H, J = 1.0 and 7.0 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 28.5, 80.4, 100.6, 122.2, 115.8, 118.1, 120.4, 122.0, 125.5, 132.8, 164.7. IR (KBr): ν 3133, 2974, 2929, 1705, 1541, 1499, 1392, 1364, 1353, 1304 cm^{-1}. HRMS (TOF-MS) calcd for $C_{13}H_{16}NO_2$ $(M + H)^+$ 218.11756, found 218.11736.

Indolizine-2-carbonitrile (**2e**): 0.13 g, 30% yield; yellow solid, mp 69−70 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.55−6.62 (m, 2H), 6.74 (dd, 1H, J = 7.0 and 9.1 Hz), 7.32 (d, 1H, J = 9.1 Hz), 7,62 (s, 1H), 7.83 (d, 1H, J = 7.0 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 97.4, 102.6, 113.2, 116.6, 117.6, 119.6, 119.8, 125.2, 132.8. IR (KBr): ν 2226, 1638, 1520, 1488, 1458, 1369, 1349, 1309, 1250, 1219, 1188, 1141, 1121 cm^{-1} HRMS (FT-MS): calcd for $C_9H_7N_2$ $(M + H)^+$ 143.06037, found 143.06023.

1H,2H,3H-Cyclopenta[b]indolizin-1-one (**2f**): 0.33g, 65% yield; yellow solid, mp 156−157 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.95−2.99 (m, 2H), 3.03−3.07 (m, 2H), 6.44 (s, 1H), 6.51 (td, 1H, J = 1.1 and 7.0 Hz), 6.65 (ddd, 1H, J = 0.8, 6.6, and 9.3 Hz), 7.31 (d, 1H, J = 9.3 Hz), 7.63 (dd, 1H, J = 1.0 and 7.0 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 20.0, 41.4, 92.0, 112.1, 119.0, 121.8, 122.8, 129.5, 139.1, 147.9, 198.8. IR (KBr): ν 3128, 2921, 1678, 1631, 1529, 1472,

DOI: 10.1021/jo502471q
J. Org. Chem. 2015, 80, 2529−2538

1451 cm^{-1}. HRMS (FT-MS): calcd for $C_{11}H_{10}NO$ $(M + H)^+$172.07569, found 172.07581.

*Methyl pyrrolo[1,2-a]quinoline-2-carboxylate (**2g**):* 0.30 g, 45% yield; white solid, mp 110−111 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 3.89 (s, 3H), 6.88 (d, 1H, *J* = 1.4 Hz), 6.97−7.01 (m, 1H), 7.22−7.26 (m, 1H), 7.31−7.37 (m, 1H), 7.47−7.54 (m, 1H), 7.61 (dd, 1H, *J* = 1.1 and 7.7 Hz), 7.88 (d, 1H, *J* = 8.5 Hz), 8.36 (s, 1H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 51.7, 103.9, 114.6, 116.1, 119.2, 119.3, 120.5, 124.5, 125.0, 128.5, 129.0, 131.5, 133.2, 165.6. IR (KBr): ν 1711, 1528, 1500, 1435, 1421 cm^{-1} HRMS (FT-MS): calcd for $C_{14}H_{12}NO_2$ $(M + H)^+$ 226.08626, found 226.08634.

*Methyl 7-methylindolizine-2-carboxylate (**2h**):* 0.22 g, 39% yield; white solid, mp 111−112 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 2.22 (s, 3H), 3.85 (s, 3H), 6.33 (dd, 1H, *J* = 7.2 and 1.1 Hz), 6.64 (s, 1H), 7.06 (s, 1H), 7.64 (d, 1H, *J* = 1.1 Hz), 7.72 (d, 1H, *J* = 7.2 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 21.2, 51.6, 98.9, 115.4, 115.4, 115.5, 118.2, 119.8, 125.0, 128.4, 133.3, 165.9. IR (KBr): ν 1716, 1545.9, 1491, 1446, 1403, 1301, 1318, 1215 cm^{-1}. HRMS (FT-MS): calcd for $C_{11}H_{12}NO_2$ $(M + H)^+$ 190.08626, found 190.08624.

*Methyl 7-ethylindolizine-2-carboxylate (**2i**):* 0.27 g, 44% yield; pale yellow solid, mp 49−50 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 1.20 (t, 3H, *J* = 7.5 Hz), 2.52 (q, 2H, *J* = 7.5 Hz), 3.85 (s, 3H), 6.37 (dd, 1H, *J* = 1.6 and 7.2 Hz), 6.67 (s, 1H), 7.07 (s, 1H), 7.69−7.70 (m, 1H), 7.74 (d, 1H, *J* = 7.2 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 14.4, 28.3, 51.6, 99.2, 114.4, 115.4, 116.7, 119.8, 125.2, 133.4, 134.6, 165.9. IR (KBr): ν 3133, 2963, 1701, 1544, 1492, 1473, 1459, 1438, 1406, 1359, 1323, 1222 cm^{-1}. HRMS (TOF-MS): calcd for $C_{12}H_{14}NO_2$ $(M + H)^+$ 204.1024, found 204.1019.

*Methyl 6-methylindolizine-2-carboxylate (**2j**):* 0.22 g, 39% yield; white solid, mp 82−83 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 2.18 (s, 3H), 3.85 (s, 3H), 6.51 (d, 1H, *J* = 9.0 Hz), 6.74 (s, 1H), 7.24 (d, 1H, 9.0 Hz), 7.61 (s, 1H), 7.68 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 18.5, 51.6, 100.4, 115.7, 119.3, 119.9, 121.9, 122.8, 131.9, 165.9. IR (KBr): ν 1716, 1545, 1491, 1445, 1403, 1300, 1318, 1215, 1096 cm^{-1} HRMS (FT-MS): calcd for $C_{11}H_{12}NO_2$ $(M + H)^+$ 190.08626, found 190.08620.

*Methyl 5-methylindolizine-2-carboxylate (**2k**):* 0.23 g, 41% yield, white solid, mp 59−60 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 2.46 (s, 3H), 3.88 (s, 3H), 6.38 (d, 1H, *J* = 6.6 Hz), 6.67 (dd, 1H, *J* = 6.6 and 9.1 Hz), 6.88 (d, 1H, *J* = 1.4 Hz), 7.29 (d, 1H, *J* = 9.1 Hz), 7.69 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 18.6, 51.6, 101.2, 111.5, 113.2, 118.1, 118.7, 119.7, 133.2, 133.7, 165.9. IR (KBr): ν 1717, 1546, 1500, 1438, 1422, 1382, 1360, 1218, 1154 cm^{-1}. HRMS (TOF-MS): calcd for $C_{11}H_{12}NO_2$ $(M + H)^+$ 190.0863, found 190.0868.

*Methyl 5-bromoindolizine-2-carboxylate (**2l**):* 0.29 g, 38% yield; pale yellow solid, mp 83−84 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 3.88 (s, 3H), 6.55−6.61 (m, 1H), 6.82−6.84 (m, 1H), 6.99 (s, 1H), 7.37 (d, 1H, *J* = 8.7 Hz), 8.07 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 51.8, 103.0, 114.8, 116.5, 117.2, 118.5, 119.5, 120.1, 134.5, 165.4. IR (KBr): ν 1723, 1623, 1543, 1506, 1493, 1203, 1230 cm^{-1}. HRMS (FT-MS): calcd for $C_{10}H_9{}^{79}BrNO_2$ $(M + H)^+$ 253.98112 and $C_{10}H_9{}^{81}BrNO_2$ $(M + H)^+$ 255.97907, found 253.98166 (^{79}Br) and 255.97961 (^{81}Br).

Preparation of 1-(Indolizin-2-yl)ethan-1-one (2m).[36] To a solution of pyridine-2-carboxaldehyde (0.101 g, 1 mmol) and methyl vinyl ketone (0.075 g, 1 mmol) in CH_3CN/H_2O (2 mL, 99/1 v/v) was added TMSOTf (1 mmol) at 0 °C. Then, the reaction mixture was warmed to room temperature and was stirred for 12 h. After that, the reaction medium was diluted with diethyl ether (10 mL) and a saturated solution of $NaHCO_3$ (10 mL) was added. The organic layer was separated, and the aqueous layer was washed twice with diethyl ether (5 mL). The organic layers were combined, washed with water (2 × 15 mL) and , brine (1 × 15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (silica flash, ethyl acetate 5−40% in hexane) to furnish a pure material as a white solid: 0.079 g, 35% yield. ^1H NMR (250 MHz, $CDCl_3$): δ 2.51 (s, 3H), 6.50 (td, 1H, *J* = 1.1 and 7.0 Hz), 6.64 (ddd, 1H, *J* = 0.8, 6.5, and 8.9 Hz), 6.75 (s, 1H), 7.31 (d, 1H, *J* = 8.9 Hz), 7.72 (d, 1H, *J* = 1.1 Hz), 7.81 (dd, 1H, *J* = 0.8 and 7.0 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 27.8, 99.7, 112.8, 115.4, 118.6, 120.7, 125.7, 128.6, 133.3, 195.2.

Preparation of *6H,7H,8H,9H*-Pyrido[1,2-*a*]indol-9-one (2n). To a solution of pyridine-2-carboxaldehyde (0.107 g, 1 mmol) in THF/H_2O (2 mL 1/1 v/v) were added DMAP (0.060 g, 0.49 mmol) and 2-cyclohexenone (0.25 mL, 2.6 mmol). Then the reaction mixture was stirred at room temperature for 96 h. After that, the solvent was removed under low vacuum pressure and the crude material was purified by column chromatography (silica flash, ethyl acetate 50−100% in hexane) to give the desired MBH adduct: 0.092 g, 40% yield; yellow solid, mp 87−88 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 2.23−2.33 (m, 2H), 2.58−2.63 (m, 2H), 2.94 (t, 2H, *J* = 6.2 Hz), 6.54 (td, 1H, *J* = 1.0 and 7.0 Hz), 6.64 (ddd, 1H, *J* = 1.0, 6.4, and 8.9 Hz), 6.73 (s, 1H), 7.34 (d, 1H, *J* = 8.9 Hz), 7.61 (dd, 1H, *J* = 1.0 and 7.0 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 21.2, 23.8, 38.8, 95.5, 112.4, 118.2, 121.2, 122.4, 123.4, 132.2, 133.1, 196.2. IR (KBr): ν 3073, 2944, 2869, 2832, 1661, 1537, 1465, 1448, 1416, 1363, 1331, 1304, 1245, 1214 cm^{-1}. HRMS (FT-MS): calcd for $C_{12}H_{12}NO$ $(M + H)^+$ 186.09134, found 186.09156.

Preparation of Indolizin-2-ylmethanol (2o). To a solution of **2a** (0.176 g, 1.0 mmol) in dry THF (5 mL) was added $LiAlH_4$ (2.0 mmol) at 0 °C. After 1 h at 0 °C, the solution was warmed to room temperature and stirred for 1 h. Then, distilled water (0.5 mL) was added carefully, the mixture was filtered through a plug of K_2CO_3 and Celite, and the cake was washed with dry THF. The solution was concentrated, and the crude material was purified by column chromatography (silica flash, ethyl acetate 60−100% in hexane) to furnish **2o**, as a solid (0.122 g): yield 83%, white solid, mp 106−107 °C. ^1H NMR (250 MHz, DMSO-d_6): δ 4.55 (d, 2H, *J* = 5.5 Hz), 4.91 (t, 1H, *J* = 5.5 Hz), 6.29 (s, 1H), 6.45 (td, 1H, *J* = 0.9 and 6.9 Hz), 6.62 (ddd, 1H, *J* = 0.9, 6.9, and 9.0 Hz), 7.31 (d, 1H, *J* = 9.0 Hz), 7.42 (s, 1H), 8.17 (dd, 1H, *J* = 0.9 and 6.9 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 59.3, 98.1, 110.5, 110.9, 117.4, 119.2, 125.3, 129.4, 133.3 ppm. IR (film): ν 3407, 2924, 2866, 1685, 1654, 1560, 1541, 1508, 1458, 1362, 1292, 1137 cm^{-1}. HRMS (TOF-MS): calcd for $C_9H_{10}NO$ $(M + H)^+$ 148.07569, found 148.07558.

General Procedure for the Partial Hydrogenation of Indolizines. To a mixture of indolizines **2a−n** (0.25 mmol) in CH_3OH (5 mL) was added PtO_2 (0.02 mmol, 10 mol %), and the atmosphere was replaced with N_2, followed by H_2. The reaction mixtures were stirred vigorously for 2−48 h at room temperature. Then, the reaction medium was filtrated through a plug of Celite and the filtrate was concentrated. The crude product was purified by column chromatography (silica flash, ethyl acetate 10−40% in hexane) to give the corresponding tetrahydroindolizines.

*Methyl 5,6,7,8-tetrahydroindolizine-2-carboxylate (**3a**):* 0.042 g, yield 93%; white solid, mp 73−74 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 1.74−1.83 (m, 2H), 1.87−1.96 (m, 2H), 2.72 (t, 2H, *J* = 6.1 Hz), 3.75 (s, 3H), 3.91 (t, 2H, *J* = 12.1 Hz), 6.21 (d, 1H, *J* = 1.3 Hz), 7.11 (d, 1H, *J* = 1.3 Hz) ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 21.3, 23.3, 23.7, 46.0, 51.1, 105.8, 115.1, 124.4, 130.4, 165.8 IR (KBr): ν 3122, 2945, 1700, 1559, 1521, 1466, 1437, 1391, 1204 cm^{-1}. HRMS (TOF-MS): calcd for $C_{10}H_{14}NO_2$ $(M + H)^+$ 180.1024, found 180.1020.

*Ethyl 5,6,7,8-tetrahydroindolizine-2-carboxylate (**3b**):* 0.044 g, yield 91%; colorless oil. ^1H NMR (250 MHz, $CDCl_3$): δ 1.29 (t, 3H, *J* = 7.1 Hz), 1.73−1.83 (m, 2H), 1.86−1.96 (m, 2H), 2.71 (t, 2H, *J* = 6.5 Hz), 3.90 (t, 2H, *J* = 12.0 Hz), 4.22 (q, 3H, *J* = 7.1 Hz), 6.21 (s, 1H), 7.11 (d, 1H, *J* = 1.7 Hz), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 14.6, 21.2, 23.2, 23.7, 45.9, 59.6, 115.5, 124.2, 130.3, 165.4, IR (film): ν 2945, 2868, 1704, 1561, 1519, 1470, 1455, 1406, 1383, 1322 cm^{-1}. HRMS (FT-MS): calcd for $C_{11}H_{16}NO_2$ $(M + H)^+$ 194.11756, found 194.11777.

*Butyl 5,6,7,8-tetrahydroindolizine-2-carboxylate (**3c**):* 0.052 g, yield 95%; yellow oil. ^1H NMR (250 MHz, $CDCl_3$): δ 0.92 (t, 3H, *J* = 7.3 Hz), 1.33−1.48 (m, 2H), 1.59−1.71 (m, 2H), 1.73−1.83 (m, 2H), 1.85−1.95 (m, 2H), 2.71 (t, 2H, *J* = 6.1 Hz), 3.90 (t, 2H, *J* = 12.0 Hz), 4.17 (t, 3H, *J* = 6.6 Hz), 6.21 (s, 1H), 7.10 (d, 1H, *J* = 1.7 Hz), ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 13.9, 19.4, 21.2, 23.2, 23.7, 31.1, 45.9, 63.5, 105.7, 115.5, 124.2, 130.3, 165.4 ppm. IR (film): ν 2955, 2871, 1704, 1561, 1519, 1470, 1456, 1407, 1389, 1322 cm^{-1}. HRMS (ESI): calcd for $C_{13}H_{20}NO_2$ $(M + H)^+$ 222.14886, found 222.14897.

DOI: 10.1021/jo502471q
J. Org. Chem. 2015, 80, 2529−2538

*tert-Butyl 5,6,7,8-tetrahydroindolizine-2-carboxylate (**3d**):* 0.052 g, yield 95%; white solid, 63−64 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.50 (s, 9H), 1.75−1.80 (m, 2H), 1.89−1.95 (m, 2H), 2.71 (t, 2H, J = 6.1 Hz), 3.89 (t, 2H, J = 5.9 Hz), 6.17 (s, 1H), 7.04 (s, 1H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 21.3, 23.3, 23.8, 28.6, 46.0, 79.3, 105.8, 117.3, 124.0, 130.1, 164.9 ppm. IR (film): ν 2977, 2964, 2937, 2877, 1697, 1520, 1473, 1457, 1448, 1400, 1390, 1367, 1324, 1222 cm^{-1}. HRMS (FT-MS): calcd for $C_{13}H_{20}NO_2$ $(M + H)^+$ 222.14886, found 222.14864.

*5,6,7,8-Tetrahydroindolizine-2-carbonitrile (**3e**):* 0.016 g, yield 40%, purple oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.75−1.85 (m, 2H), 1.88−1.98 (m, 2H), 2.71 (t, 2H, J = 6.1 Hz), 3.91 (t, 2H, J = 12.1 Hz), 6.04 (s, 1H), 6.95 (d, 1H, J = 1.6 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 20.9, 23.0, 23.5, 46.1, 92.0, 107.8, 117.6, 126.2, 130.8 ppm. IR (film): ν 3116, 2953, 2897, 2861, 2219, 1556, 1514, 1470, 1455, 1384, 1193, 1153, 1126 cm^{-1}. HRMS (FT-MS): calcd for $C_9H_{11}N_2$ $(M + H)^+$ 147.09168, found 147.09166.

*1H,2H,3H,5H,6H,7H,8H-cyclopenta[b]indolizin-1-one (**3f**):* 0.040 g, yield 91%; white solid, mp 141−142 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.72−1.81 (m, 2H), 1.88−1.98 (m, 2H), 2.71−2.76 (m, 6H), 3.81 (t, 2H, J = 6.1 Hz), 5.90 (s, 1H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 20.2, 20.9, 23.3, 24.2, 41.1, 43.7, 98.4, 126.0, 137.5, 158.6, 196.6 ppm. IR (KBr): ν 2953, 2890, 1661, 1556, 1538, 1517, 1488, 1471, 1455 cm^{-1}. HRMS (FT-MS): calcd for $C_{11}H_{14}NO$ $(M + H)^+$ 176.10699, found 176.10690.

*Methyl 5H,6H-pyrrolo[1,2-a]quinoline-8-carboxylate (**3g**):* 0.038 g, yield 67%, colorless oil. ^{1}H NMR (250 MHz, acetone-d_6): δ 2.91 (s, 4H) 3.76 (s, 3H), 6.36 (s, 1H), 7.15−7.21 (m, 1H), 7.32−7.38 (m, 2H), 7.65−7.68 (m, 1H), 7.91 (d, 1H, J = 1.6 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 22.2, 26.9, 51.4, 106.7, 115.8, 116.9, 119.9, 125.4, 127.9, 128.6, 129.4, 130.8, 136.0, 165.5 ppm. IR (film): ν 3054, 2987, 1707, 1524, 1497, 1438, 1422 cm^{-1}. HRMS (FT-MS): calcd for $C_{14}H_{14}NO_2$ $(M + H)^+$ 228.10191, found 228.10195. Note: this product and the starting material present the same R_f value.

*Methyl 7-methyl-5,6,7,8-tetrahydroindolizine-2-carboxylate (**3h**):* 0.038 g, yield 79%; white solid, mp 83−84 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.06 (d, 1H, J = 6.4 Hz), 1.50−1.67 (m, 1H), 1.82−1.92 (m, 2H), 2.21−2.32 (m, 1H), 2.84 (dd, 1H, J = 4.5 and 16.0 Hz), 3.75 (s, 3H), 3.85 (td, 1H, J = 4.5 and 11.4 Hz), 3.97−4.06 (m, 1H), 6.19 (s, 1H), 7.12 (s, 1H, J = 1,6 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 21.5, 28.0, 31.6, 31.7, 45.4, 51.1, 105.6, 115.4, 124.2, 130.5, 165.8 ppm. IR (KBr): ν 2954, 2893, 1705, 1517, 1447, 1386 cm^{-1}. HRMS (FT-MS): calcd for $C_{11}H_{16}NO_2$ $(M + H)^+$ 194.11755, found 194.11762.

*Methyl 7-ethyl-5,6,7,8-tetrahydroindolizine-2-carboxylate (**3i**):* 0.042 g, yield 81%; white solid, mp 50−51 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.94 (t, 3H, J = 7.2 Hz), 1.37−1.43 (m, 2H), 1.60−1.63 (m, 2H), 1.97−2.02 (m, 1H), 2.22−2.32 (m, 1H), 2.85−2.92 (m, 1H), 3.76 (s, 3H), 3.85−3.89 (m, 1H), 4.00−4.05 (m, 1H), 6.20 (s, 1H), 7.12 (s, 1H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 11.5, 28.7, 29.5, 34.7, 45.5, 51.1, 105.7, 115.4, 124.1, 130.6, 165.8 ppm. IR (KBr): ν 2959, 2925, 2961, 2854, 1710, 1559, 1521, 1465, 1437, 1394, 1245, 1207 cm^{-1}. HRMS (TOF-MS): calcd for $C_{12}H_{18}NO_2$ $(M + H)^+$ 208.1333, found 208.1338.

*Methyl 6-methyl-5,6,7,8-tetrahydroindolizine-2-carboxylate (**3j**):* 0.038 g, yield 79%; colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.05 (d, 3H, J = 6.6 Hz), 1.37−1.48 (m, 1H), 1.87−2.00 (m, 2H), 2.59−2.73 (m, 1H), 2.79−2.89 (m, 1H), 3.37−3.46 (m, 1H), 3,69 (dd, 1H, J = 4.8 and 12.2 Hz), 3.75 (s, 3H), 6.22 (s, 1H), 7.09 (s, 1H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 19.0, 22.7, 29.6, 29.7, 51.1, 52.7, 105.6, 115.3, 124.2, 130.0, 165.8 ppm. IR (KBr): ν 2954, 2928, 2851, 1710, 1561, 1465, 1440, 1394, 1210 cm^{-1}. HRMS (TOF-MS): calcd for $C_{11}H_{16}NO_2$ $(M + H)^+$ 194.1176, found 194.1172.

*Methyl 5-methyl-5,6,7,8-tetrahydroindolizine-2-carboxylate (**3k**):* 0.039 g, yield 80%, colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.45 (d, 3H, J = 6.5 Hz), 1.57−1.73 (m, 2H), 1.86−1.95 (m, 1H), 1.98−2.08 (m, 1H), 2.58−2.79 (m, 2H), 3.75 (s, 3H), 3.97−4.10 (m, 1H), 6.19 (s, 1H), 7.26 (d, 1H, J = 1.8 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 19.7, 22.4, 23.6, 31.8, 51.1, 51.3, 105.6, 115.0, 122.8, 130.8, 165.8 ppm. IR (KBr): ν 2954, 2928, 2851, 1710, 1561, 1465, 1440, 1394, 1210 cm^{-1}. HRMS (TOF-MS): calcd for $C_{11}H_{16}NO_2$ $(M + H)^+$ 194.1176, found 194.1170.

*1-(5,6,7,8-Tetrahydroindolizin-2-yl)ethan-1-one (**3l**):* 0.026 g, yield 65%; pale yellow solid, mp 57−58 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.74−1.82 (m, 2H), 1.91−1.97 (m, 2H), 2.32 (s, 1H), 2.72 (t, 2H, J = 6.2 Hz), 3.92 (t, 2H, J = 6.0 Hz), 6.22 (s, 1H), 7.09 (d, 1H, J = 1.4 Hz) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 21.2, 23.2, 23.7, 27.1, 46.1, 104.9, 124.4, 125.4, 131.1, 193.7 ppm. IR (KBr): ν 2942, 2869, 1649, 1518, 1556, 1469, 1441, 1399, 1383 cm^{-1}. HRMS (FT-MS): calcd for $C_{10}H_{14}NO$ $(M + H)^+$ 164.10699, found 164.10680.

*1H,2H,3H,4H,6H,7H,8H,9H-pyrido[1,2-a]indol-9-one (**3m**):* 0.042 g, yield 90%; white solid, mp 106−107 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.72−1.82 (m, 2H), 1.89−1.99 (m, 2H), 2.04−2.14 (m, 2H), 2.37−2.43 (m, 2H), 2.72 (t, 2H, J = 6.3 Hz), 2.65 (t, 2H, J = 6.2 Hz), 3.76 (t, 2H, J = 6.1 Hz), 6.16 (s, 1H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 21.0, 21.5, 23.4, 23.6, 23.8, 38.1, 43.3, 101.1, 119.9, 131.0, 142.4, 194.2 ppm. IR (KBr): ν 2954, 2890, 1743, 1635, 1592, 1573, 1473, 1438 cm^{-1}. HRMS (ESI): calcd for $C_{12}H_{16}NO$ $(M + H)^+$ 190.12264, found 190.12292.

General Protocol for the Full Hydrogenation of Indolizines. To a mixture of indolizine (1 mmol) in CH_3OH/TFA (5 mL, 1/1 v/v) was added PtO_2 (0.1 mmol, 10 mol %), and the solution was placed in a glass autoclave. The air was removed by flushing a stream of H_2. The internal pressure was adjusted to 5 bar of H_2, before being reduced to 1 bar by carefully releasing a stop valve. This procedure was repeated three times, and finally the vessel was pressurized to 5 bar. The reaction mixture was stirred vigorously for 4 h. After the hydrogen gas was carefully vented, the solution was filtrated through a plug of Celite and the solution was concentrated. Then the crude material was diluted with CH_2Cl_2 (10 mL) and neutralized with a saturated solution of $NaHCO_3$ (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were combined, washed with brine (1 × 30 mL), dried with anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (silica flash, methanol 0−5% in dichloromethane) to furnish the required indolizidines.

*Methyl octahydroindolizine-2-carboxylate (**4a**):* 0.143 g, yield 78%; pale green oil. ^{1}H NMR (500 MHz, C_6D_6): δ 0.98−1.05 (m, 1H), 1.18−1.26 (m, 1H), 1.36−1.39 (m, 1H), 1.49−1.58 (m, 4H), 1.69−1.74 (m, 1H), 1.88−1.91 (m, 2H), 2.06 (t, 1H, J = 9.1 Hz), 2.60 (qd, 1H, J = 2.1 and 9.1 Hz), 2.88−2.90 (m, 1H), 3.33 (s, 3H), 3.46 (dd, 1H, J = 2.1 and 9.1 Hz) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 24.3, 25.2, 30.6, 35.2, 39.8, 52.1, 52.9, 56.8, 64.6, 175.9 ppm. IR (film): ν 2932, 2854, 2785, 2753, 2725, 1739, 1436, 1383, 1341, 1266, 1175 cm^{-1}. HRMS (TOF-MS): calcd for $C_{10}H_{18}NO_2$ $(M + H)^+$ 184.1338, found 184.1345.

*Ethyl octahydroindolizine-2-carboxylate (**4b**):* 0.158 g, yield 80%; pale green oil. ^{1}H NMR (600 MHz, C_6D_6): δ 0.95 (t, 3H, J = 7.2 Hz), 0.98−1.03 (m, 1H), 1.24−1.28 (m, 1H), 1.36−1.39 (m, 1H), 1.52−1.57 (m, 4H), 1.70−1.74 (m, 1H), 1.88−1.96 (m, 2H), 2.08 (t, 1H, J = 9.6 Hz), 2.60−2.65 (m, 1H), 2.91−2.92 (m, 1H), 3.52 (dd, 1H, J = 2.4 and 9.6 Hz), 3.96 (q, 2H, J = 7.2 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.6, 25.0, 25.9, 31.2, 35.5, 40.4, 53.0, 57.2, 60.8, 64.7, 175.0 ppm. IR (film): ν 2932, 2856, 2786, 2754, 2726, 1737, 1449, 1384, 1370, 1341, 1278, 1182 cm^{-1}. HRMS (TOF-MS): calcd for $C_{11}H_{20}NO_2$ $(M + H)^+$ 198.1489, found 198.1494.

*tert-Butyl octahydroindolizine-2-carboxylate (**4c**):* 0.207 g, yield 92%; pale green oil. ^{1}H NMR (600 MHz, C_6D_6): δ 0.98−1.05 (m, 1H), 1.22−1.28 (m, 1H), 1.36−1.37 (m, 10H), 1.51−1.58 (m, 4H), 1.71−1.75 (m, 1H), 1.88−1.92 (m, 2H), 2.11 (t, 1H, J = 9.1 Hz), 2.64 (qd, 1H, J = 2.3 and 9.1 Hz), 2.91−2.92 (m, 1H), 3.52 (dd, 1H, J = 2.3 and 9.1 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.4, 25.3, 28.3, 30.7, 35.4, 40.7, 53.0, 56.7, 64.6, 80.3, 174.7 ppm. IR (film): ν 2975, 2932, 2857, 2785, 2752, 1732, 1449, 1367, 1331, 1321, 1279, 1262, 1216, 1153 cm^{-1}. HRMS (TOF-MS): calcd for $C_{13}H_{24}NO_2$ $(M + H)^+$ 226.1802, found 226.1807.

*Methyl 7-methyloctahydroindolizine-2-carboxylate (**4d**):* 0.171 g, yield 87%; pale green oil. ^{1}H NMR (600 MHz, C_6D_6): δ 0.83 (d, 3H, J = 6.4 Hz), 0.90−0.99 (m, 2H), 1.21−1.28 (m, 1H), 1.36−1.40 (m, 1H), 1.49−1.60 (m, 2H), 1.74 (td, 1H, J = 2.6 and 11.2 Hz),

DOI: 10.1021/jo502471q
J. Org. Chem. 2015, 80, 2529−2538

1.87−1.90 (m, 2H), 2.06 (t, 1H, J = 9.1 Hz), 2.64 (qd, 1H, J = 2.1 and 9.1 Hz), 2.87−2.90 (m, 1H), 3.46 (dd, 1H, J = 2.1 and 9.1 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.5, 31.8, 34.7, 35.4, 39.8, 40.8, 51.7, 52,5, 57.0, 64.6, 175.5 ppm. IR (film): ν 2950, 2923, 2871, 2850, 2793, 1742, 1456, 1435, 1376, 1333, 1202, 1191 cm^{-1}. HRMS (TOF-MS): calcd for $C_{11}H_{20}NO_2$ $(M + H)^+$ 198.1489, found 198.1494.

*Methyl 5-methyloctahydroindolizine-2-carboxylate (**4e**):* 0.168 g, yield 85%, pale green oil. ^{1}H NMR (600 MHz, C_6D_6): δ 1.01 (d, 3H, J = 6.2 Hz) 1.09−1.25 (m, 3H), 1.35−1.38 (m, 1H), 1.53−1.58 (m, 2H), 1.61−1.67 (m, 1H), 1.78−1.83 (m, 1H), 1.88−1.91 (m, 2H), 2.01 (t, 1H, J = 9.2 Hz), 2.61 (qd, 1H, J = 2.4 and 9.2 Hz), 3.65 (dd, 1H, J = 2.4 and 9.2 Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.6, 25.2, 31.3, 34.7, 35.6, 40.0, 51.7, 54.9, 58.9, 65.0, 175.5 ppm. IR (film): ν 2951, 2930, 2851, 2790, 1750, 1450, 1455, 1370 cm^{-1}. HRMS (ESI): calcd for $C_{11}H_{20}O_2N$ $(M + H)^+$ 198.1489, found 198.1495.

Preparation of (Octahydroindolizin-2-yl)methanol (4f). To a mixture of indolizine **2o** (0.029 g, 0.20 mmol) in CH_3OH (5 mL) was added Rh/Al_2O_3 (0.003 g, 10% m/m), and the atmosphere was replaced with N_2, followed by H_2. The reaction mixture was stirred vigorously for 6 h at room temperature. Then, the solution was filtered through a Celite plug, and the filtrate was concentrated. The crude product was purified by column chromatography (silica flash, methanol 10% in dichloromethane) to furnish a pure material, as a yellow oil (0.030 g, 98%). ^{1}H NMR (250 MHz, $CDCl_3$): δ major isomer, cis 3.02−2.98 (m, 2H), minor isomer, trans 2.86 (d, 2H, J = 8.1 Hz), 3.14−3.20 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ major isomer, *cis* 25.3, 30.9, 34.2, 36.7, 53.0, 58.4, 64.9, 67.5, minor isomer, trans 25.3, 30.8, 34.4, 37.5, 53.1, 58.4, 63.6, 66.0 ppm. IR (film): ν 3404, 2932, 2857, 2795, 2730, 1471, 1450, 1385, 1331, 1317, 1272, 1264, 1227, 1190, 1140 cm^{-1}. HRMS (ESI): calcdfor $C_9H_{18}NO$ $(M + H)^+$ 156.1383, found 156.1388.

■ ASSOCIATED CONTENT

Supporting Information

Text and figures giving general information and ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for F.C.: coelho@iqm.unicamp.br.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the Fapesp and CNPq for financial support (Process Fapesp 2013/07600-3). B.V.M.T. thanks the CNPq for a fellowship, and J.T.M.C. thanks the Fapesp for a fellowship (Process 2012/21809-0). The authors thank Prof. Cláudio F. Tormena for NMR suggestions and discussions and Nicolas Schwab for HRMS analyses.

■ REFERENCES

(1) (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139−165. (b) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 191−222.

(2) (a) Kim, N.-S.; Choi, J.-R.; Cha, J. K. *J. Org. Chem.* **1993**, *58*, 7096−7099. (b) Martín, R.; Murruzzu, C.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2005**, *70*, 2325−2328.

(3) Zhang, S.; Xu, L.; Miao, L.; Shu, H.; Trudell, M. L. *J. Org. Chem.* **2007**, *72*, 3133−3136.

(4) Pourashraf, M.; Delair, P.; Rasmussen, M. O.; Greene, A. E. *J. Org. Chem.* **2000**, *65*, 6966−6972.

(5) Sugimoto, K.; Toyoshima, K.; Nonaka, S.; Kotaki, K.; Ueda, H.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 7168−7171.

(6) Dinsmore, A.; Mandy, K.; Michael, J. P. *Org. Biomol. Chem.* **2006**, *4*, 1032−1037.

(7) Movassaghi, M.; Ondrus, A. E. *Org. Lett.* **2005**, *7*, 4423−4426.

(8) For some recent reviews concerning the synthesis of indolizidines, see: (a) Bhat, C.; Tilve, S. G. *RSC Adv.* **2014**, *4*, 5405−5452. (b) Chakraborty, I.; Jana, S. *Synthesis* **2013**, 3325−3331. (c) Gómez-SanJuan, A.; Sotomayor, N.; Lete, E. *Beilstein J. Org. Chem.* **2013**, *9*, 313−322. (d) Lazzaroni, R.; Settambolo, R. *Chirality* **2011**, *23*, 730−735. (e) Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Eur. J.* **2009**, *15*, 7808−7821. (f) Agarwal, S.; Cammerer, S.; Filali, S.; Frohner, W.; Knoll, J.; Krahl, M. P.; Reddy, K. R.; Knolker, H. J. *Curr. Org. Chem.* **2005**, *9*, 1601−1614.

(9) For some examples for the synthesis of tetrahydroindolizidines, see: (a) Bowie, A. L., Jr.; Trauner, D. *J. Org. Chem.* **2009**, *74*, 1581−1586. (b) Ghosh, S. K.; Buchanan, S. G.; Long, Q. A.; Wie, Y.; Al-Rashid, Z. F.; Sklenicka, H. M.; Hsung, R. P. *Tetrahedron* **2008**, *64*, 883−893. (c) Rocchiccioli, S.; Settambolo, R.; Lazzaroni, R. *J. Organomet. Chem.* **2005**, *690*, 1866−1870. (d) Marchalin, T.; Cvopova, K.; Pham-Huu, D. P.; Chudik, M.; Kozisek, J.; Svoboda, I.; Daich, A. *Tetrahedron Lett.* **2001**, *42*, 5663−5667. (e) Lehmann, T.; Gmeiner, P. *Heterocycles* **2000**, *53*, 1371−1378. (f) Gmeiner, P.; Lerche, H. *Heterocycles* **1990**, *31*, 9−12. (g) Wang, M. D.; Alper, H. *Tetrahedron Lett.* **1995**, *36*, 6855−6858. (h) Tanis, S. P.; Raggon, J. W. *J. Org. Chem.* **1987**, *52*, 819−827.

(10) For some examples concerning the preparation of indolizines, see: (a) Pandya, A. N.; Fletcher, J. T.; Villa, E. M.; Agrawal, D. K. *Tetrahedron Lett.* **2014**, *55*, 6922−6924. (b) Mamedov, V. A.; Kalinin, A. A.; Samigulina, A. I.; Mironova, E. V.; Krivolapov, D. B.; Gubaidulin, A. T.; Rizvolapov, D. B. *Tetrahedron Lett.* **2013**, *54*, 3348−3352. (c) Muthusaravanan, S.; Perumal, S.; Yogeeswari, P.; Sriram, D. *Tetrahedron Lett.* **2010**, *51*, 6439−6443. (d) Kucukdisli, M.; Opatz, T. *J. Org. Chem.* **2013**, *78*, 6670−6676. (e) Chung, L.-H.; Wong, C.-Y *Organometallics* **2013**, *32*, 3583−3586. (f) Zhang, C.; Zhang, H.; Zhang, L.; Wen, T. B.; He, X.; Xia, H. *Organometallics* **2013**, *32*, 3738−3743. (g) Lee, J. H.; Kim, I. *J. Org. Chem.* **2013**, *78*, 1283−1288. (h) Jung, Y.; Kim, I. *Tetrahedron* **2012**, *68*, 8198−8206. (i) Zhu, H.; Stockigt, J.; Yu, Y.; Zou, H. *Org. Lett.* **2011**, *13*, 2792−2794. (j) Smith, C. R.; Bunnelle, E. M.; Rhodes, A. J.; Sarpong, R. *Org. Lett.* **2007**, *9*, 1169−1171. (k) Rotaru, A. V.; Druta, I. D.; Oeser, T.; Muller, T. J. J. *Helv. Chim. Acta* **2005**, *88*, 1798−1812. (l) Fang, X.; Wu, Y.-M; Denga, J.; Wang, S.-W. *Tetrahedron* **2004**, *60*, 5487−5493. (m) Bora, U.; Saikia, A.; Boruah, R. C. *Org. Lett.* **2003**, *5*, 435−438. (n) Katritzky, A. R.; Qiu, G. F.; Yang, B. Z.; He, H. Y. *J. Org. Chem.* **1999**, *64*, 7618−7621.

(11) (a) Bode, M. L.; Kaye, P. T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1809−1813. (b) Bode, M. L.; Kaye, P. T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2612−2613.

(12) Singh, V.; Hutait, S.; Batra, S. *Eur. J. Org. Chem.* **2010**, 3684−3691.

(13) Cunha, S. M. D.; Oliveira, R. G.; Vasconcellos, M. L. A. A. *J. Braz. Chem. Soc.* **2013**, *24*, 432−438.

(14) (a) Basavaiah, D.; Rao, A. J. *Chem. Commun.* **2003**, 604−605. (b) Basavaiah, D.; Veeraraghavaiah, G.; Badsara, S. S. *Org. Biomol. Chem.* **2014**, *12*, 1551−1556.

(15) (a) Crawford, J. J.; Young, W. B. Alkylated Piperazine Compounds as Inihibitors of BTK Activity and Their Preparation. PCT Patent WO 067277, May 10, 2013; SciFinder Scholar 2013:728485. (b) Payne, L. J.; Downham, R.; Sibley, G. E. M.; Edwards, P.; Davies, G. M. 2-Oxo-2-(2-Phenyl-5,6,7,8-tetrahydroindolizin-3-yl)acetamide Derivatives as Antifungal Agents and Their Preparation. PCT WO 145,968, December 4, 2008; SciFinder Scholar 2008:1450870. (c) Shen, S.; Sun, L.; Xie, Y. Benzimidazolyl-pyridine Compounds for Inflammation and Immune-related Uses. PCT Patent WO 112,093, October 4, 2007; SciFinder Scholar 2007:115254. (d) Gmeiner, P.; Huebner, H.; Bettinetti, L.; Schlotter, K. Preparation of 2-indolizinecrboxiamides and Related Compounds as Central Nervous System Agents. PCT Patent WO 015,737, February 16,

DOI: 10.1021/jo502471q
J. Org. Chem. 2015, 80, 2529−2538

2006; SciFinder Scholar 2006:151134. (e) Mignani, S.; Nemecek, C. Preparation and Antiviral Activity of Indolizine Derivatives, PCT WO 9,964,419, December 16, 1999; SciFinder Scholar 1999:795812. (f) Sabb, A. L. Saturated and Unsaturated Pyridazino[4,5-b]indolizines Useful as Antidementia Agents, US Patent 5,756,501, May 26, 1998; SciFinder Scholar 1998:331565.
(16) Soldatova, S. A.; Alarkon, J. A.; Mamyrbekova, Z. A.; Kryvenko, L. I.; Ntaganda, Z.; Ryashentseva, M. A.; Soldatenkov, A. T. *Chem. Heterocycl. Compd.* **1994**, *30*, 331−334.
(17) Ortega, N.; Tang, D.-T. D; Urban, S.; Zhao, D.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 9500−9503.
(18) Zaporozhets, O. B.; Ryashentseva, M. A.; Polosin, V. M.; Poponova, R. V. *Russ. Chem. Bull.* **1993**, *42*, 1209−1210.
(19) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074−2075.
(20) Alonso, F.; Yus, M.; Albaladejo, M. J. *Chem. Eur. J.* **2013**, *19*, 5242−5245.
(21) Coelho, F.; Almeida, W. F.; Mateus, C. R.; Lopes, E. C. S.; Rossi, R. C.; Silveira, G. P. C.; Pavam, C. H. *Tetrahedron* **2002**, *58*, 7437−7447.
(22) For details about the Morita−Baylis−Hillman reaction and its application in organic synthesis, see: (a) Shi, M.; Wang, F.-J.; Zhao, M.-X.; Wei, Y. In *The Chemistry of the Morita-Baylis-Hillman Reaction*; RSC Publishing: Cambridge, U.K., 2011. (b) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447−5674. (c) de Souza, R. O. M. A.; Miranda, L. S. M. *Mini-Rev. Org. Chem.* **2010**, *7*, 212−220. (d) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511−4574. (e) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581−1588. (f) Almeida, W. P.; Coelho, F. *Quim. Nova* **2001**, *23*, 98−101.
(23) Appel, R. *Angew. Chem., Int. Ed.* **1975**, *14*, 801−811.
(24) Kim, J. T.; Gevorgyan, V. *J. Org. Chem.* **2005**, *70*, 2054−2059.
(25) Nishimura, S. In *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; Wiley: Hoboken, NJ, 2011.
(26) Wolfe, S.; Schlegel, H. B.; Whangbo, M.-H.; Bernardi, F. *Can. J. Chem.* **1974**, *52*, 3787−3792.
(27) Gribble, G. W.; Nelson, R. B. *J. Org. Chem.* **1973**, *38*, 2831−2834.
(28) Claridge, T. D. W. One-Dimensional Techniques. In *High Resolution NMR Techniques in Organic Chemistry*, 2nd ed.; Bäckvall, J.-E., Baldwin, J. E., Williams, R. M., Eds.; Elsevier: Amsterdam, 2009; Tetrahedron Organic Chemistry Series Vol. *27*, pp 101−116.
(29) Armarego, W. L. *J. Chem. Soc. B* **1966**, 191−194.
(30) Dippy, J. F. J.; Hughes, S. R. C.; Rozanski, A. *J. Chem. Soc.* **1959**, 2492−2498.
(31) (a) Fraser, M.; McKenzie, S.; Reid, H. *J. Chem. Soc. B* **1966**, 44−48. (b) Swinbourne, F. J.; Hunt, J. H.; Klinkert, G. *Adv. Heterocycl. Chem.* **1978**, *23*, 103−170. (c) Wiench, J. W.; Stefaniak, L.; Webb, G. A. *Magn. Reson. Chem.* **1994**, *32*, 373−379.
(32) Chastanet, J.; Roussi, G. *J. Org. Chem.* **1985**, *50*, 2910−2914.
(33) (a) Mi, X.; Luo, S.; Cheng, J.-P. *J. Org. Chem.* **2005**, *70*, 2338−2341. (b) Zhao, S.; Chen, Z. *Synth. Commun.* **2005**, *35*, 121−127. (c) Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 692−700.
(34) (a) Cai, Y.; Gao, G. *Monatsh. Chem.* **2007**, *138*, 1163−1167. (b) Basavaiah, D.; Krishnamacharyulu, M.; Rao, A. J. *Synth. Commun.* **2000**, *30*, 2061−2069.
(35) Lin, Y.-S.; Liu, C.-W.; Tsai, T. Y. R. *Tetrahedron Lett.* **2005**, *46*, 1859−1861.
(36) (a) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159−1162. (b) Basavaiah, D.; Rao, A. J. *Chem. Commun.* **2003**, 604−605.

DOI: 10.1021/jo502471q
J. Org. Chem. 2015, 80, 2529−2538