Origin of the Diastereoselectivity of the Heterogeneous Hydrogenation of a Substituted Indolizine

Rodrigo A. Cormanich, Lucas A. Zeoly, Hugo Santos, Nilton S. Camilo, Michael Bühl, and Fernando Coelho*

ABSTRACT: In this work, the stereoselective heterogeneous hydrogenation of a tetrasubstituted indolizine was studied. Partial hydrogenation products were obtained in three steps from a substituted pyridine-2-carboxaldehyde prepared from commercial pyridoxine hydrochloride. The hydrogenation of the indolizine ring was shown to be diastereoselective, forming trans-6b and cis-9. Theoretical calculations (ab initio and DFT) were used to rationalize the unusual trans stereoselectivity for 6b, and a keto−enol tautomerism under kinetic control has been proposed as the source of diastereoselectivity.

Naturally occurring 5,6,7,8-tetrahydroindolizinones, bicyclic compounds characterized by a pyrrole ring fused to a 6-membered saturated chain, a bridgehead nitrogen atom, and a ketone moiety, are of rare occurrence in nature, even though their indolizidine saturated analogues are abundant in alkaloid chemistry.

For instance, the isolation of the first natural 5,6,7,8-tetrahydroindolizinone was reported only in 1997, when polygonatine B (1) was isolated from the liliaceous plant Polygonatum sibiricum (Figure 1) and from Polygonatum kingianum (2). Polygonatine A (3), the hydroxymethyl parent of both 1 and 2, was also isolated from P. sibiricum. Both 1 and 2 exhibited antimicrobial and antifungal activities against a range of microorganisms.

Furthermore, (−)-rhazinic (4), an alkaloid containing the 5,6,7,8-tetrahydroindolizin-5-one motif, showed an antitumor activity similar to that of taxol (Figure 1).

Unlike 5,6,7,8-tetrahydroindolizinones, whose preparations have been achieved by efficient procedures in the literature, there are only a few protocols reported for 5,6,7,8-tetrahydroindolizinone synthesis. More specifically, the synthesis of compounds containing a 5,6,7,8-tetrahydroindolizin-8-one core (also named 6,7-dihydro-8(5H)-indolizinone) has been scarcely explored, with most of the approaches relying on Friedel−Crafts acylation. To the best of our knowledge, there are no reports on 5,6,7,8-tetrahydroindolizinone preparation directly through partial hydrogenation of an indolizine.

Figure 1. Naturally occurring 5,6,7,8-tetrahydroindolizinone derivatives.
In this work, we describe the results of a highly trans diastereoselective heterogeneous hydrogenation reaction of the tetrasubstituted indolizine 5 to prepare polyfunctionalized 5,6,7,8-tetrahydroindolizin-8-one 6 (Scheme 1). This transformation was rationalized by theoretical calculations, which suggested a keto−enol tautomerism as the source of the observed stereoselectivity, favoring the kinetic product. The starting material for our synthetic route was pyridoxine hydrochloride—also known as vitamin B6—which, despite its polyfunctionalized structure, is a low-cost compound (>US $1 per gram). We envisaged that the presence of hydroxyl groups of different reactivities in vitamin B6 could potentially be explored for the preparation of new tetrahydroindolizinone and tetrahydroindolizine motifs.

The synthetic route developed for the synthesis of the 5,6,7,8-tetrahydroindolizinone 6 was carefully planned to avoid chromatographic purification in most of its steps. Furthermore, most of the sequence was carried out on a multigram scale through low cost and efficient reactions. Thus, functionalized pyridine-2-carboxaldehyde 7 was prepared in six steps and 77% overall yield by using a quite robust, modified procedure reported several decades ago by Korytnyk et al. (Scheme 1). The presence of the seven-membered cyclic acetal in 7 is essential, since it is key to the observed diastereoselectivity in the heterogeneous hydrogenation step, as will be discussed later. No chromatographic purification was required for the preparation of 7, which was sufficiently pure by NMR spectrum to be used in the next reaction step.

The Morita–Baylis–Hillman (MBH) reaction of compound 7 with methyl acrylate, a key step of our approach, was performed using a protocol developed by our laboratory involving the use of ultrasound to speed up the reaction. Adduct 8 was obtained in 85% yield after 64 h, and the crude product was used in the next reaction step without further purification. Then, we turned our attention to prepare indolizine 5. Several literature methodologies describe the synthesis of indolizines from MBH adducts. We initially opted to test some of them, and the best result was achieved by heating the MBH adduct to 100 °C in acetic anhydride medium. Some byproducts were formed in this step, and chromatographic purification was necessary to obtain pure 5 in 65% yield.

Once indolizine 5 was prepared, the performance of the partial hydrogenation reaction was evaluated by screening reaction parameters such as heterogeneous catalysts, H2 pressures, and solvents (see the Supporting Information for more details). When Rh/Al2O3 was used as a catalyst in ethyl acetate at 80 bar of H2 pressure and room temperature, starting material 5 was fully consumed after 48 h, furnishing a mixture of three main compounds (as determined by 1H NMR). Compound 6b could be separated and isolated in 30% yield, while alcohol 9 was obtained as an inseparable mixture (see the Supporting Information for full structural assignment) (Scheme 2).

Compound 6b and the mixture containing 9 were fully characterized by 1H, 13C{1H} NMR, 1H−1H COSY, 1H−13C HSQC, and 1H−13C HMBC experiments, and their relative
stereochemistries were assigned using $J_{HH}$ obtained directly from $^1$H NMR spectra$^{16}$ and NOE values$^{17}$ obtained from NOESY experiments (see the Supporting Information for details).

Curiously, compound 6b was not further reduced under high pressures of H$_2$. Also, this compound shows a trans relationship between the hydrogen atoms at the 6–7 ring junction, and the other possible diastereomer (6a), which would have a cis relationship between these hydrogen atoms, was not observed. The hydrogenation of each individual double bond is expected to occur by cis addition of H$_2$. However, it is intriguing that the second double bond hydrogenation occurs preferentially at the opposite face of the first hydrogenation step to furnish 6b.

A plausible mechanistic rationale accounting for the formation of the products of this reaction is shown in Scheme 3.

Benzyl hydrogenolysis should occur quickly, even at low hydrogen pressure.$^{18}$ Indeed, the disappearance of the typical aromatic protons of the benzyl group in the crude $^1$H NMR spectrum was observed after only 1 h of reaction at 1 atm of H$_2$. Debenzylated intermediate 10 could be hydrogenated in either one of the two double bonds of the 6-membered ring. Supposing that the double bond in the $\alpha$ position to the nitrogen atom is hydrogenated preferentially (C5–C6 reduction), there is formation of enol 11, which in turn can furnish compound 6b via keto–enol tautomerism. Catalytic hydrogenation of either 11 or 12, which would come from C7–C8 reduction, could then furnish alcohol 9. Since formation of the stereogenic center at position 7 occurs with the aromatic protons of the benzyl group in the crude $^1$H NMR spectrum was observed after only 1 h of reaction at 1 atm of H$_2$.

To elucidate the reason for the observed stereoselectivity of the hydrogenation step, theoretical calculations were carried out for compound 6 for both cis (6a) and trans (6b) relative stereochemistries (see the Supporting Information for details).

For both compounds 6a and 6b, the conformer of type 1 is the most stable at the B3LYP-D3/aug-cc-pVdz level in EtOAc. Its geometrical representations are shown in Figure 2 and considered for further comparative calculations between these two diastereomers using DFT functionals and ab initio methods (Table S1, Supporting Information).

![Figure 2. Geometrical representations for the global minima of 6a and 6b obtained at the B3LYP-D3/aug-cc-pVdz level in EtOAc, using the IEF-PCM implicit solvent model.](image)

The ab initio methods show that electron correlation is an important factor to be taken into account, since the HF method shows the opposite result in comparison to MP2, Grimme’s spin-component-scaled (SCS)$^{19}$ MP2 and MP4 methods, which indicate that 6a should be more stable than 6b. Similarly, the B3LYP functional shows the opposite result, indicating that 6b should be 0.55 kcal mol$^{-1}$ more stable than 6a ($\Delta G$ values, Table S1, Supporting Information). When Grimme’s D3 dispersion correction$^{20}$ is applied to the B3LYP method, 6a becomes more stable, hence indicating both electron correlation and dispersion corrections should be important parameters to account for the energy difference between 6a and 6b.

Based on these results, we applied Truhlar’s M06, M06-2X, and M11 functionals$^{20,21}$ and Grimme’s B2PLYP functional$^{22}$ including D3 dispersion correction for the latter. These functionals showed a considerable increase in $\Delta G$ values favoring 6a in comparison to B3LYP-D3. By considering the calculated $\Delta G$ values for these functionals, the approximate ratio between 6a and 6b (6a:6b) is calculated to be of 1:1 for B3LYP-D3, 2:1 for M06-2X, 3:1 for M06, 4:1 for M11, and 7:1 for B2PLYP-D3. Although these functionals show a higher stability for 6a, they are not in complete agreement with the experimental result, since 6a was not observed in any proportion. The MP2 $ab$ initio method shows a 6a:6b ratio of 10:1 (1.38 kcal mol$^{-1}$; Table S1, Supporting Information). However, the SCS-MP2, which is considered an improvement for the MP2 method, shows a smaller 5:1 ratio. Although of high accuracy, the SCS-MP2 approach cannot replace the CCSD(T) model, which has been termed as “the gold standard” in the literature, mainly when applied together with the CBS approximation. The CCSD(T) method, which scales as N$^7$ (N = basis set), was shown to be prohibitively expensive to be applied for 6a and 6b. However, we could apply the MP4(SDQ) method$^{27}$ and the DLPNO-CCSDT(T)/aug-cc-pVTZ$^{28–30}$ level, which may be considered the highest levels applied in this work. The MP4(SDQ) showed a Gibbs free energy preference for 6a of 1.82 kcal mol$^{-1}$ (Table S1, Supporting Information). Such an energy difference would correspond to a ratio higher than 20:1. However, the DLPNO-CCSD(T) showed only a slight preference for 6a of 0.19 kcal mol$^{-1}$, which increases to 0.82 kcal mol$^{-1}$ when thermal Gibbs free energy corrections from the M11 functional are added. Thus, even high-level ab initio methods diverge in the energy difference between 6a and 6b, showing that 6a should be slightly more stable, even though it could not be observed experimentally. It is worth mentioning that keto–enol tautomerism has been shown to be a challenge for high level ab initio methods and DFT calculations in the gas phase and implicit solvent even for simpler molecular systems in previous benchmark studies.$^{31}$

Thus, although the cis isomer should be the most stable, the keto–enol tautomerism can have a high barrier in this molecular system, with the formation of the trans isomer controlled kinetically instead of thermodynamically. Indeed, it was observed that carboxylic acids can catalyze the keto–enol tautomerism and decrease the Gibbs free energy barrier of keto–enol interconversion by as much as 45 kcal mol$^{-1}$. Because the reaction in this work is being carried out in EtOAc, some residual acetic acid (AcOH) may be present in the reaction mixture, catalyzing the reaction, decreasing the barrier height, and possibly making 6b the favored kinetic product.

The keto tautomer (6a or 6b, see the Supporting Information) is more stable than the enol tautomer (11) by as much as 19 kcal mol$^{-1}$ (M11/aug-cc-pvDZ), and the uncatalyzed energy barrier in the stepwise mechanism can be as high as $\sim$50–60 kcal mol$^{-1}$. In order to evaluate the kinetic product, we obtained the reaction barriers for formation of 6a and 6b from 11 catalyzed by AcOH (Figure 3). These calculations were carried out at the M11/aug-cc-pvDZ level, since this theoretical level showed similar results to the
DLPNO-CCSD(T)/aug-cc-pVTZ (Table S1, Supporting Information). Such calculations showed a $\Delta G^\ddagger$ value of 15.50 kcal/mol for 6b and 17.19 kcal/mol for 6a; hence, the barrier for 6a is 1.69 kcal/mol higher than that for 6b. Thus, 6b is the kinetic product and 6a is the thermodynamic one. Because 6a is not observed experimentally, these results suggest that the observed product 6b may be preferentially formed under kinetic control. Quantitatively, our computed difference in the activation barriers is probably somewhat underestimated, because it would correspond to a 6a:6b distribution of 5:95 at room temperature. Qualitatively, however, our results provide evidence for this reaction being under kinetic control, and this may be the reason why the diastereomer with cis stereochemistry is not observed experimentally.

The present work explored the heterogeneous hydrogenation of a polyfunctionalized indolizine (S), which was prepared by using a straightforward two-step sequence based on a Morita–Baylis–Hillman reaction with a known pyridine-2-carboxaldehyde. The partial hydrogenation step was shown to be highly diastereoselective, forming trans ketone 6b in 30% yield and cis alcohol 9 as an inseparable mixture of unassigned compounds. The intriguing experimental preference of cis diastereomers in heterogeneous hydrogenation reactions. The present work may help guide future experiments for the exploration of keto–enol tautomerism to efficiently select thermodynamic/kinetic diastereomers in heterogeneous hydrogenation reactions.

#### EXPERIMENTAL SECTION

**General Procedures.** All chemicals and solvents were of analytical grade, purchased from commercial sources, and used without further purification unless otherwise stipulated.

Unless otherwise noted, all reactions were performed under an ambient atmosphere in oven-dried open-flask glassware with magnetic stirring. Reaction progress was monitored by analytical thin-layer chromatography (TLC) performed on precoated silica gel 60 F254 (5–40 μm thickness) plates. The TLC plates were visualized with UV light (254 nm) and/or potassium permanganate or sulfuric vanillin followed by heating. When necessary, reaction products were purified by *flash* column chromatography using silica gel (230–400 mesh).

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Nuclear magnetic resonance spectra were recorded in deuterated solvents at room temperature at 250, 400, 500, and 600 MHz. Data are reported as follows: chemical shift (δ) in ppm, multiplicity, coupling constant (J), and integrated intensity. Abbreviations to denote the multiplicity of a particular signal are s (singlet), bs (broad singlet), d (doublet), t (triplet), dd (double doublet), ddd (double double doublet), dddd (double double double doublet), and m (multiplet).

The high-resolution mass spectrometric analyses (HRMS) were performed in a Q-TOF instrument, equipped with ESI ionization source operating in the positive mode (ESI(+)-MS). The samples were injected by direct infusion in a 40 μL-min$^{-1}$ flow. The following parameters were used: 3 kV capillary voltage, 20 V cone voltage, source temperature of 120 °C, and nebulization gas flow of 0.5 L·min$^{-1}$. Before every analysis, the instrument was calibrated with an H$_3$PO$_4$ solution (0.005% in H$_2$O/CH$_3$CN 1:1) from m/z 100 to 1000. Hydrogenation reactions were carried out in a suitable reactor fitted with a mechanic stirrer and a system for measuring and controlling both pressure and temperature (Parr Instruments Series 4590 Micro Stirred Reactor).

Reactions under ultrasound were carried out in an ultrasonic cleaner UNIQUE model GA 1000 (1000 W, 25 kHz).

Compounds were named according to IUPAC rules using the MarvinSketch 20.11 software. Compounds S1–S5 are the intermediates for the preparation of aldehyde 7.

**Preparation of Compound S1.** 5-[(Benzyloxy)-4-(hydroxy-methyl)-6-methylpyridin-3-yl]methanol (S1). To a round-bottomed flask containing pyridoxine hydrochloride (2.00 g, 9.73 mmol) and anhydrous potassium carbonate (3.0 equiv, 4.03 g, 29.2 mmol) was added anhydrous acetone (160 mL) under stirring. The mixture was heated to reflux using a preheated silicone oil bath (at ~90 °C) for 1 h. Then, benzyl bromide (1.0 equiv, 1.16 mL, 9.73 mmol) was added and the reaction mixture was stirred under reflux for 3 h. After this time, the reaction was allowed to cool to room temperature and then was quenched by addition of distilled water (100 mL). The mixture was extracted with EtoAc (4 × 30 mL), and the combined organic phases were dried with anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The resulting solid was recrystallized from EtOH to afford the desired product as a brown crystalline solid in 83% yield (2.09 g, 8.06 mmol). Mp = 111–113 °C (lit., $^{13}$H NMR (250 MHz, DMSO-d$_6$): δ 8.27 (s, 1H), 7.54–7.33 (m, 5H), 5.25 (t, J = 5.5 Hz, 1H, OH), 5.15 (t, J = 5.5 Hz, 1H, OH), 4.89 (s, 2H), 4.67 (d, J = 5.5 Hz, 2H), 4.60 (d, J = 5.5 Hz, 2H), 2.42 (s, 3H).$^{1}$C(1H) NMR (62.9 MHz, DMSO-d$_6$): δ 151.2, 150.7, 143.7, 139.7, 135.4, 128.5 (2C), 128.19 (2C), 128.18, 75.8, 58.6, 53.9, 19.4. HRMS (ESI/Q-TOF) m/z: Calcd for C$_7$H$_8$NO, [M + H$^+$]: 260.1281, found 260.1281.

**Preparation of Indolizine 5.** 9-[(Benzyloxy)-3,3,8-trimethyl-1H,3H,5H-1,3-dioxepino[5,6-c]pyridine (S2). To a round-bottomed flask, S1 (3.41 g, 13.2 mmol) and 2,2-dimethoxypropane (180 mL) were added. The mixture was then heated to reflux using a...
preheated silicone oil bath (at ∼90 °C) until complete dissolution of the starting material. Then, t-p-toluenesulfonic acid monohydrate (0.05 equiv, 125.1 mg, 0.658 mmol) was added to the solution under stirring, and the reaction mixture was maintained under these conditions for 14 h. After this time, the reaction mixture was allowed to cool to room temperature and then quenched by adding distilled H$_2$O (50 mL) and Na$_2$SO$_4$. The resulting mixture was extracted with CHCl$_3$ (4 × 50 mL), and the combined organic phases were dried with anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to furnish crude acetate as a viscous brown oil in quantitative yield (4.15 g). This compound was sufficiently pure to be used in the next step without further purification. $^1$H NMR (400 MHz, CDCl$_3$): $delta$ 7.25–7.35 (m, 5H), 5.41 (s, 2H), 4.74–4.66 (m, 4H), 2.45 (s, 3H), 1.43 (s, 6H). $^{13}$C{1H} NMR (100 MHz, CDCl$_3$): $delta$ 151.6, 145.2, 135.5, 134.7, 133.1, 132.3, 129.02, 128.96 (2C), 128.4 (2C), 128.3 (2C), 127.7 (2C), 127.6 (2C), 127.5 (2C), 127.2 (2C). HRMS (ESI/Q-TOF) m/z: Calcd for C$_{18}$H$_{20}$NO$_3$ [M + H]$^+$: 314.1384, found 314.1383.

9-(Benzoxyl)-3,3-dimethyl-1H,3H,5H-[1,3]dioxepino[5,6-c]-pyridin-7-ium-7-olate (53) $^{13}$ methylene chloride (100 mL), and then quenched with 10% (m/v) aqueous solution of NaHCO$_3$ (2.06 mL). The organic phase was dried with anhydrous Na$_2$SO$_4$ and filtered, and the solvent was removed under reduced pressure to give crude acetate as a viscous yellow oil in quantitative yield (4.25 g). This compound was sufficiently pure to be used in the next step without further purification. $^1$H NMR (400 MHz, CDCl$_3$): $delta$ 7.30–7.34 (m, 5H), 5.01 (s, 2H), 4.88 (s, 2H), 4.78 (s, 2H), 1.44 (s, 6H). $^{13}$C{1H} NMR (100 MHz, CDCl$_3$): $delta$ 191.1, 153.7, 144.1, 143.6, 143.5, 140.6, 135.9, 129.0, 128.9 (4C), 128.4 (2C), 128.3 (2C), 127.7 (2C), 127.6 (2C), 127.5 (2C), 127.2 (2C). HRMS (ESI/Q-TOF) m/z: Calcd for C$_{18}$H$_{20}$NO$_3$ [M + H]$^+$: 314.1387, found 314.1384.

Methyl 2-{[9-(Benzoxyl)-3,3-dimethyl-1H,3H,5H-[1,3]dioxepino[5,6-c]-pyridin-7-yl)(hydroxy)methyl}prop-2-enoate (8). Aldehyde 7 (1.47 g, 4.91 mmol) and 1,4-diazabicyclo[2.2.2]octane (DABCO, 0.65 equiv, 342 mg, 3.05 mmol) were added to a 250 mL round-bottomed flask. Then, methyl acrylate (20 equiv, 8.5 mL, 93.8 mmol) was added to the reaction mixture without magnetic stirring, and the reaction flask was fitted with a rubber septum and connected with a gas bubbler (with silicone oil). At room temperature, the mixture was sonicated in an ultrasound bath for 64 h (the water bath in the ultrasound equipment was kept at room temperature). After this time, the excess methyl acrylate was removed under reduced pressure (alternatively, excess methyl acrylate can be recovered via distillation). The crude product was redissolved in EtOAc (40 mL), and the solution was washed with saturated aqueous solution of NH$_4$Cl (4 × 20 mL). The organic phase was dried with anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to afford crude MBH adduct 8 as a yellow oil in 85% yield (1.66 g, 4.17 mmol). Compound 8 was sufficiently pure to be used in the next step without further purification. $^1$H NMR (250 MHz, CDCl$_3$): $delta$ 8.10 (s, 1H), 7.42–7.35 (m, 5H), 6.28 (s, 1H), 5.85 (s, 1H), 5.61 (s, 1H), 4.96–4.70 (m, 6H), 3.67 (s, 3H), 1.47 (s, 3H), 1.46 (s, 3H). $^{13}$C{1H} NMR (63 MHz, CDCl$_3$): $delta$ 166.7, 152.1, 149.3, 142.2, 142.0, 141.5, 136.3, 135.7, 128.9 (2C), 128.8, 128.3 (2C), 126.7, 126.7, 103.0, 76.5, 76.8, 67.2, 60.9, 52.1, 23.8. HRMS (ESI/Q-TOF) m/z: Calcd for C$_{18}$H$_{20}$NO$_3$ [M + H]$^+$: 314.1755, found 314.1754.

Methyl 2-{[9-(Benzoxyl)-3,3-dimethyl-1H,3H,5H-[1,3]dioxepino[5,6-c]-pyridin-7-yl)methyl}prop-2-enoate (54). In a round-bottomed flask, S3 (4.15 g, 13.1 mmol) was dissolved in anhydrous acetic anhydride (66 mL, 0.20 mol·L$^{-1}$) under stirring at room temperature and heated to 70 °C using a preheated silicone-oil bath for 1 h. [CAUTION: This transformation, also known as the Bockelheide reaction, may proceed rather exothermically and vigorously. A reflux condenser should be adapted to the flask.] Then, the reaction mixture was allowed to cool to room temperature, and the solvent was removed under vacuum to the flask. The resulting mixture was extracted with EtOAc (3 × 50 mL), and the combined organic phases were dried with anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to furnish crude acetate as a viscous yellow oil in quantitative yield (5.03 g). This compound was sufficiently pure to be used in the next step without further purification. $^1$H NMR (500 MHz, CDCl$_3$): $delta$ 8.13 (s, 1H), 7.42–7.35 (m, 5H), 5.19 (s, 2H), 4.85 (s, 2H), 4.81 (s, 4H), 2.06 (s, 3H), 1.44 (s, 6H). $^{13}$C{1H} NMR (126 MHz, CDCl$_3$): $delta$ 170.7, 150.5, 147.7, 142.7, 141.8, 136.0, 135.9, 128.8 (2C), 128.7, 128.2 (2C), 128.2, 76.9, 62.4, 61.7, 58.9, 23.6, 20.9. HRMS (ESI/Q-TOF) m/z: Calcd for C$_{18}$H$_{20}$NO$_3$ [M + H]$^+$: 314.1694, found 358.1694.

9-(Benzoxyl)-3,3-dimethyl-1H,3H,5H-[1,3]dioxepino[5,6-c]-pyridin-7-ium-7-olate (55) $^{13}$ NaH (60% dispersion in mineral oil, 0.338 mmol) were carefully added to the reaction mixture under a nitrogen atmosphere, carefully dissolved in 80 mL of hexane (20:80), and heated to 103.0 °C under stirring. When the reaction was quenched with 10% (m/v) aqueous solution of NaHCO$_3$ (2.06 mL), the mixture was filtered, and concentrated under reduced pressure to give the desired N-oxide as a viscous yellow oil in quantitative yield (0.883 g, 2.32 mmol). $^1$H NMR (250 MHz, CDCl$_3$): $delta$ 7.74 (d, $J$ = 1.5 Hz, 1H), 7.49 (s, 1H), 7.48–7.32 (m, 6H), 6.90 (s, 1H), 5.14 (s, 2H), 4.76 (s, 2H), 4.67 (s, 2H), 3.88 (s, 3H), 1.43 (s, 6H). $^{13}$C{1H} NMR (63 MHz, CDCl$_3$): $delta$ 165.6, 145.7, 136.9, 128.9 (2C), 128.2 (2C). HRMS (ESI/Q-TOF) m/z: Calcd for C$_{18}$H$_{20}$NO$_3$ [M + H]$^+$: 316.1543, found 316.1543.
Heterogeneous Hydrogenation of Indolizine 5. Indolizine 5 (120 mg, 0.315 mmol) was dissolved in ethyl acetate (5 mL), Rh/AI-O (12 mg, 10% w/w) was added to the solution, and the atmosphere was replaced with H2 (80 bar) in a hydrogenation reactor. The reaction mixture was stirred vigorously for 48 h at room temperature. Then, the reaction medium was purged with N2 and filtered through a plug of Celite, and the filtrate was concentrated.

Analysis of the crude by 1H NMR showed three main products, which were purified by column chromatography (silica gel, EtOAc/hexane 30:70) to afford product 6b (27 mg, 0.094 mmol) in 30% yield as a colorless oil and a mixture containing 9 (27 mg, 0.091 mmol) as an oil.

Methyl (5aRS,11aSR)-3,3-Dimethyl-11-oxo-1H,3H,5H,5aH,6H,11-H,11aH-{[3]}dioxepino[5,6-f]indolizine-9-carboxylate (6b). 1H NMR (600 MHz, C6D6): δ 7.71 (d, J = 1.7 Hz, 1H), 6.94 (d, J = 1.7 Hz, 1H), 4.59 (dd, J = 12.7, 3.5 Hz, 1H), 3.71 (dd, J = 12.7, 9.8 Hz, 1H), 3.55 (s, 3H), 3.14 (dd, J = 11.8, 10.1 Hz, 1H), 2.92 (dd, J = 11.8, 3.1 Hz, 1H), 2.65 (dd, J = 12.3, 4.2 Hz, 1H), 2.36 (t, J = 12.3 Hz, 1H), 1.88 (ddd, J = 12.3, 9.8, 3.5 Hz, 1H), 1.56 (tddd, J = 12.3, 10.1, 4.2, 3.1 Hz, 1H), 1.23 (s, 3H), 1.21 (s, 3H). 13C{1H} NMR: δ 186.0, 164.2, 130.9, 118.2, 114.2, 101.6, 62.3, 60.9, 52.6, 51.0, 46.7, 42.2, 25.0, 24.8. HRMS (ESI/Q-TOF) m/z: Calcd for C15H22NO5 [M + Na]+ 276.0842, found 276.0829.

Computational Details. Conformers of compounds 6a and 6b were located through a Monte Carlo conformational search at the MMFF level with the Spartan 14 program,35 using a 1 kcal-mol⁻¹ threshold and 5000 K initial temperature in the simulated-annealing algorithm. Optimizations and frequency calculations were carried out at the B3LYP-D3/aug-cc-pVDZ level using the Gaussian 09 program, revision D.01.36 The global minima of 6a and 6b were reoptimized by using several DFT functional methods and the MP2 ab initio methods and the aug-cc-pVDZ basis set. MP4 single point calculations were carried out over the M11/aug-cc-pVDZ optimized geometries, and the enthalpy and Gibbs free energies were obtained from this same functional to add to MP2, MP4, and B2PLYP-D3 potential energies. DLPNO-CCSD(T)/aug-cc-pVTZ calculations were run over the M11/aug-cc-pVDZ optimized geometries using the ORCA 4.2.1 program and were also corrected with the enthalpy and Gibbs free energies obtained from this same level.37

The authors declare no competing financial interest.

Acknowledgments

The authors are grateful to FAPESP for the financial support of this research. The authors also thank FAPESP for the fellowships to R.A.C. (#2008/03910-1) and for a scholarship to H.S. (#2015/09205-0) and CNPq for a scholarship to L.A.Z. and a research fellowship for F.C. (308840/2014-0, 422890/2016-2 and 301330/2016-2). L.A.Z. also thanks Capes for a scholarship. CENAPAD-SP, CESUP, and SDumont computational resources are also gratefully acknowledged.

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