Highly Regioselective Vilsmeier−Haack Acylation of Hexahydropyrroloindolizine

Babak Sayah, Nadia Pelloux-Léon, Anne Milet, Joséphine Pardillos-Guindet, and Yannick Vallée*

LEDSS, Université Joseph Fourier-CNRS, B.P. 53, 38041 Grenoble, France

Yannick.Vallee@ujf-grenoble.fr

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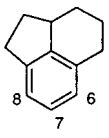
Myrmicaria ants, a genus of African Myrmicinae, produce a series of poisonous alkaloids containing the hexahydropyrroloindolizine ring system.[1] The simplest members of this new family (Scheme 1) are the ethyl propyl derivative named myrmicarin 217 (M217) and the (*Z*)- and (*E*)-ethylpropenyl derivatives M215A and M215B. The first synthesis of racemic M217[2] was reported by Schröder and Francke (which previously isolated the various natural myrmicarins),[1] and we recently described a synthesis of nonracemic (*R*)-(+)-M217.[3]

Formally, M215A,B and M217 can be regarded as derived from the unsubstituted compound **1** via two regioselective electrophilic aromatic substitutions. For instance, M217 would be formed by a regioselective ethylation on C_4, followed by the introduction of the propyl group on C_3 (Scheme 1). Alternatively, the propyl group could be first regioselectively linked to C_3, and the ethyl group entered in second. To overcome the possible problem of double alkylation (for instance, substitution by two ethyl groups) in the first step of these syntheses, as well as the possible rearrangement of the propyl cation, it would probably be more efficient to use acylation reactions, rather than alkylation reactions, each acylation being followed by a reduction step of the obtained ketone into the needed alkyl group. The obvious question is then: can some regioselectivity be expected for an acylation reaction on a substrate that looks so *quasi-symmetric*? With two goals in mind, the major one being to give a (positive) answer to this question and the other one being to determine if myrmicarins could be synthesized this way, we decided to study some acylation reactions of compound **1**.

Only a few studies have been conducted on similar questions. In the 1980s, two French teams published their results about the Friedel−Crafts acetylation of tetrahydroacenaphtene **2**, the analogue of the pyrrole



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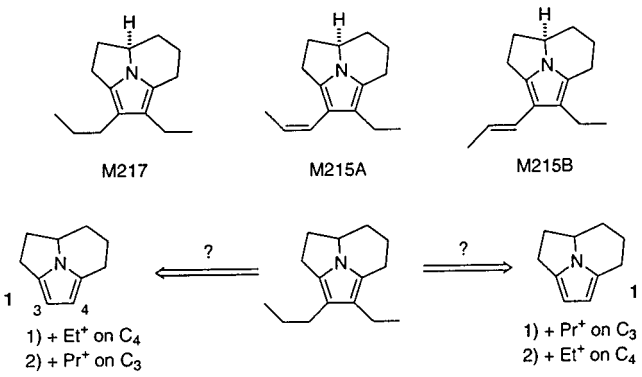
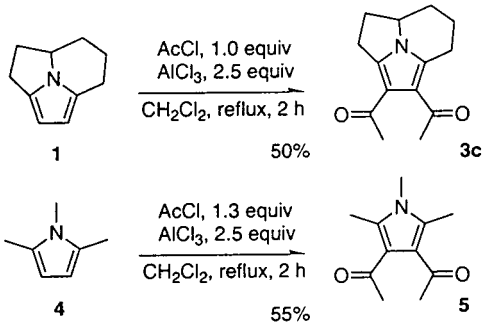
derivative **1** in the benzene family.[4] They reported only poor selectivities, generally in favor of acetylation on C_8.

Scheme 1



Scheme 2



1 **3c** **4** **5**

The authors presented steric arguments to explain their observations.[5] Furthermore, even some substitution on the poorly reactive C_7 was noticed and the results depended largely on the used conditions (including the order of introduction of the reagents!). This was not very encouraging for our particular case. However, we tested some Friedel−Crafts acetylation reactions with compound **1**.

The first results were very disappointing, but not for the reason we were expecting. When **1** was treated with acetyl chloride (1.0 equiv) in the presence of aluminum trichloride (2.5 equiv), the only isolated product (yield 50%) was the diacetylated compound **3c** (Scheme 2). Neither of the two regioisomeric monoacetylated compounds was isolated. This was not specific to the tricyclic compound **1**; when the same reaction was conducted with 1,2,5-trimethylpyrrole **4**, the obtained product was the diacetyl trimethylpyrrole **5**.[6] No traces of the monoacetyl derivative were noticed.

We were more successful with Vilsmeier−Haack reactions[7] (Table 1). For instance (entry 1), when **1** was treated with dimethylacetamide (1.0 equiv) and $POCl_3$ (1.0 equiv) in dichloroethane at room temperature for 24 h, the two regioisomers **3a**,**b** were isolated as an unseparable mixture in 70% yield. No diacetylated derivative **3c** was noticed. The ratio **3a/3b**, determined by ^{1}H NMR,

(1) Francke, W.; Schröder, F.; Walter, F.; Sinnwell, V.; Baumann, H.; Kaib, M. *Liebigs Ann.* **1995**, 965. Schröder, F.; Francke, S.; Francke, W.; Baumann, H.; Kaib, M.; Pasteels, J. M.; Daloze, D. *Tetrahedron* **1996**, *52*, 13539. Schröder, F.; Sinnwell, V.; Baumann, H.; Kaib, M. *J. Chem. Soc., Chem. Commun.* **1996**, 2139. Schröder, F.; Sinnwell, V.; Baumann, H.; Kaib, M.; Francke, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 77.

(2) Schröder, F.; Francke, W. *Tetrahedron* **1998**, *54*, 5259.

(3) Sayah, B.; Pelloux-Léon, N.; Vallée, Y. *J. Org. Chem.* **2000**, *65*, 2824.

(4) Gruber, R.; Cagniant, D.; Cagniant, P. *Bull. Soc. Chim.* **1983**, 93.

(5) Gruber, R.; Kirsch, G.; Cagniant, D. *Bull. Soc. Chim.* **1987**, 498.

(6) Bright, J. *J. Am. Chem. Soc.* **1957**, *79*, 3200.

(7) Gangjee, A.; Patel, J.; Kisliuk, R.; Gaumont, Y. *J. Med. Chem.* **1992**, *35*, 3678.

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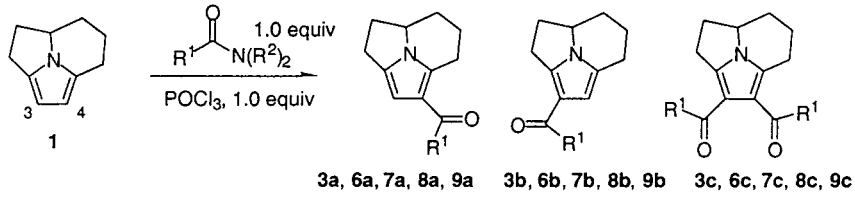
Table 1. Yields and Ratios Obtained in Vilsmeier−Haack Acylations under Different Reaction Conditions

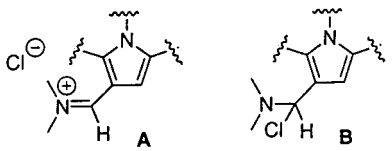


entry	R^1	R^2	solvent, T (°C), reaction time (h)	monoacylated compds, yield (%)	ratio C_4/C_3	diacylated compd, yield (%)
1	Me	Me	$C_2H_4Cl_2$, rt, 24	**3a**,**b**, 70	80/20	*a*
2	Me	Me	$C_2H_4Cl_2$, 83, 3	**3a**,**b**, 70	84/16	*a*
3	Me	Me	toluene, 83, 3	**3a**,**b**, 71	80/20	*a*
4	Me	Pr^i	$C_2H_4Cl_2$, 83, 24	**3a**,**b**, 70	70/30	*a*
5	H	Me	$C_2H_4Cl_2$, 83, 2	**6a**,**b**, 70	86/14	*a*
6	Et	Me	$C_2H_4Cl_2$, 83, 3	**7a**,**b**, 75	70/30	*a*
7	Pr^i	Me	$C_2H_4Cl_2$, 83, 24	**8a**,**b**, 65	55/45	*a*
8	Bu^t	Me	$C_2H_4Cl_2$, 83, 24	**9a**,**b**[c]	30/70[c]	*a*
9	H	Me	cyclohexane, 83, 4	**6a**,**b**, traces	*b*	**6c**, 42
10	H	Me	toluene, rt, 4	**6a**,**b**, 70	97/3	**6c**, 3
11	H	Me	toluene, 83, 2	**6a**,**b**, 53	>99/1	**6c**, 18
12	H	Me	CH_2Cl_2, 40, 3	**6a**,**b**, 72	93/7	*a*
13[d]	H	Me	CH_2Cl_2, 40, 3	**6a**,**b**, 80	86/14	*a*

[a] Not observed. [b] Not determined. [c] Not separated from byproducts. [d] Reaction with 2.0 equiv of DMF, 2.0 equiv of $POCl_3$.

was 80/20. Thus, in contrast with the results reported for the Friedel−Crafts acetylation of tetrahydroacenaphtene **2**, the observed regioselectivity largely favored the substitution on the carbon nearing the saturated six-membered ring; i.e., if we accept and extrapolate to this case the arguments presented in refs 4 and 5 on the more hindered carbon. Indeed, examination of the results presented in Table 1 indicates that the bulkier the Vislmeier reagent, whether because of its R^1 group (for instance, compare entries 2, 5, 6, 7, and 8), or because of its R^2 nitrogen substituents (compare entries 2 and 4), the more important is the proportion of the product acetylated on C_3. This confirms that C_3, nearing the five-membered ring, suffers less steric constraint than C_4.

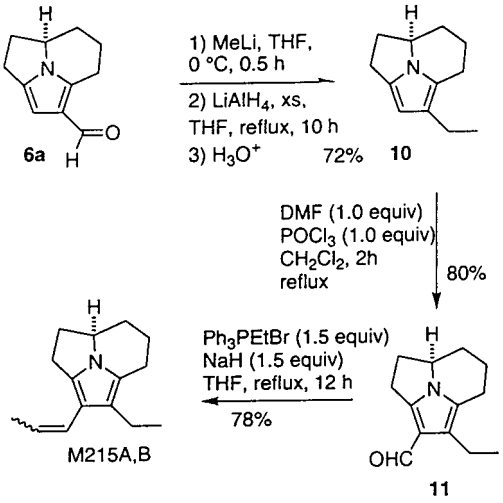
The influence of temperature for reactions conducted in dichloroethane was quite low (entries 1 and 2). In contrast, changes of the solvent had a dramatic influence on the course of the formylation reaction. The most impressive change was the exclusive formation of the diformylated product **6c** when the solvent was cyclohexane (entry 9). No traces of **6c** were noticed when the reaction was conducted in $C_2H_4Cl_2$ or CH_2Cl_2, even when 2.0 equiv of Vilsmeier reagent was used (entry 13). Our interpretation of these results is that in polar solvents the product formed in the reaction mixture, before hydrolysis, probably has the iminium structure **A**. This



positively charged species cannot undergo any further electrophilic substitution. We propose that the product is much more covalent in nonpolar solvents and might be well described by structure **B**. **B** is a neutral pyrrole bearing one more substituent, as compared to the starting tricycle **1**. Thus, **B** might be more nucleophilic than **1**. This would explain the exclusive formation of **6c**.

Toluene is slightly more polar than cyclohexane (but considerably less polar than the chlorinated solvents).

Scheme 3

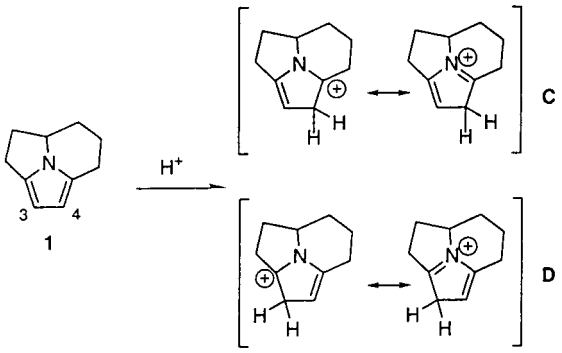


When it was used as the solvent (entry 11), the major product was monoformylated; however, some diformylated pyrrole **6c** was also isolated. What is more important here is the surprisingly high regioselectivity reached: the only isolated monoformylated compound was the isomer **6a**. As **6a** is easily separated from **6c**, this method can be regarded as useful for the synthesis of myrmicarins.

Thus, **6a** was treated with methyllithium, and in the same pot, the resulting alcoholate was reduced by $LiAlH_4$, giving the ethyl derivative **10** (Scheme 3). **10** was formylated under Vilsmeier conditions, and the obtained aldehyde was treated with the Wittig reagent obtained from ethyltriphenylphosphonium bromide. In this way, a mixture of M215A and B was obtained (ratio A(*Z*)/B(*E*): 4/1) in 45% yield from **6a**. This is the first reported synthesis of M215.

We undertook some theoretical calculations to determine why position 4 of **1** was more reactive than position 3. The population analysis through both the Mulliken and NBO schemes exhibited nearly no charge difference between the two carbons (−0.32e for C_3 against −0.33e for C_4 using the NBO scheme). Similarly, examination

Scheme 4



of molecular orbitals showed only a small difference in favor of an attack on C_4. More interestingly, a clear difference was found between the two cations resulting from the protonation of **1** on C_4 and C_3. These cations **C** and **D** mimic the cationic intermediate obtained in the first step of the Vilsmeier−Haack reaction (Scheme 4). The energy difference between **C** and **D** was found to be 3.1 kcal/mol at the B3LYP level of calculation with the 6-31G* basis set (HF: 3.3 kcal/mol; MP2:2.8 kcal/mol using the same basis set). The cation formed on the six-membered ring is more stable than the one formed on the other side. This can be interpreted in terms of the greater ring strain in the iminium form of cation **D**, with a C=N double bond included in the five-membered ring, and is consistent with our experimental findings. Thus, we propose that the regioselectivity of these Vilsmeier−Haack reactions is explained by the greater stability of the cationic intermediate resulting from an attack on C_4.

Finally, we think that the total regioselectivity observed for the formylation of **1** in toluene at 83 °C (Table 1, compare entries 10 and 11) should be interpreted as a consequence of the partial double formylation observed in this apolar solvent. The second formylation is probably easier when it creates a cationic intermediate on the six-membered ring. Thus, the intermediate resulting from a first attack on C_3 is double formylated more rapidly than the other one. This would explain why we isolated only **6a** and **6c**, and no **6b**.

Experimental Section

All commercial solvents were distilled before use. THF was distilled from sodium benzophenone ketyl under nitrogen atmosphere. Toluene was distilled from sodium under nitrogen atmosphere. Methylene chloride (CH_2Cl_2) and 1,2-dichloroethane ($C_2H_4Cl_2$) were distilled from calcium hydride under nitrogen atmosphere. Column chromatography purifications were carried out using silica gel (70−230 mesh). ^{1}H NMR spectra were recorded at 200, 300, or 500 MHz, and ^{13}C NMR spectra were recorded at 75 or 125 MHz. Peak assignments of NMR spectra were determined using DEPT and two-dimensional experiments.

(7a*R*)-1,2,5,6,7,7a-Hexahydropyrrolo[2,1,5-*cd*]indolizine (1). A suspension of $LiAlH_4$ (1.5 g, 39 mmol) in dry 1,4-dioxane (30 mL) was added to a stirred solution of (7a*R*)-5,6,7,7a-tetrahydro-1*H*-pyrrolo[2,1,5-*cd*]indolizin-2-one[3] (1 g, 6.20 mmol) in the same solvent (30 mL) under N_2 at room temperature. The resulting mixture was heated under reflux for 20 h and then cooled to 0 °C and quenched slowly with a saturated aqueous Na_2SO_4 solution. After filtration, the organic layer was dried and evaporated. Column chromatography on silica gel (pentane/CH_2Cl_2, 9:1) of the residue gave **1** (765 mg, 86% yield): $[\alpha]^{20}_D$ = +111.0 (*c* 0.50, CH_2Cl_2); ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.29−1.55 (m, 1H, H-1), 1.78−1.89 (m, 1H, H-7), 2.02−2.09 (m, 1H, H-6), 2.09−2.17 (m, 1H, H-7), 2.17−2.25 (m, 1H, H-1), 2.55−2.64 (m, 1H, H-6), 2.64−2.72 (m, 2H, H-2), 2.72−2.98 (m, 2H, H-5), 3.90−3.95 (m, 1H, H-7a), 5.85 (s, 2H, H-3 and H-4); ^{13}C NMR (75 MHz; $CDCl_3$) δ 21.5 (C-5), 22.8 (C-2), 25.3 (C-7), 30.1 (C-1), 37.9 (C-6), 55.7 (C-7a), 99.7 (C-4), 105.8 (C-3), 123.3, 132.0; MS (CI) 148 ($MH^{\cdot+}$). Anal. Calcd for $C_{10}H_{13}N$: C, 81.59; H, 8.9; N, 9.51. Found: C, 81.49; H, 8.88; N, 9.50.

(7a*R*)-3,4-Diacetyl-1,2,5,7,7a-hexahydropyrrolo[2,1,5-*cd*]-indolizine (3c). A solution of **1** (100 mg, 0.68 mmol) was added to a suspension of aluminum chloride (300 mg, 2.24 mmol) in dry CH_2Cl_2 (7 mL) and acetyl chloride (0.64 mL, 0.748 mmol). The resulting mixture was refluxed for 2 h, poured onto crushed ice, and stirred until melted. The layers were separated, and the aqueous one was extracted 3 times with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated. Column chromatography on silica gel of the residue gave pure compound **3c** (75 mg, yield: 50%): $[\alpha]^{20}_D$ = +68.6 (*c* 0.50, CH_2Cl_2); IR (NaCl) 1657 (CO) cm^{-1}; mp 152 °C; ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.23−1.38 (m, 1H, H-7), 1.71−1.78 (m, 1H, H-6), 2.02−2.09 (m, 1H, H-1), 2.09−2.17 (m, 1H, H-6), 2.17−2.22 (m, 1H, H-7), 2.38 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.63−2.73 (m, 1H, H-1), 2.73−2.79 (m, 1H, H-2), 2.97−3.00 (m, 1H, H-2), 3.00−3.05 (m, 2H, H-5), 3.88−3.91 (m, 1H, H-7a); ^{13}C NMR (75 MHz; $CDCl_3$) δ 20.5 (C-6), 21.4 (C-2), 26.0 (C-5), 27.7 (C-7), 28.6 (CH_3), 29.7 (CH_3), 35.0 (C-1), 55.2 (C-7a), 117.5, 122.1, 131.0, 138.6, 192.8 (CO), 196.2 (CO); MS (CI) 232 ($MH^{\cdot+}$). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.40; N, 6.05. Found: C, 72.75; H, 7.45; N, 6.05.

General Experimental Procedure for Vilsmeier−Haack Acylation of Compound 1. A solution of **1** (1.0 equiv) in a dry solvent was added at room temperature to a mixture of amide (1.0 equiv) and $POCl_3$ (1.0 equiv) in the same solvent. The resulting solution was stirred. The reaction was carried on until the initial product had totally disappeared on TLC. Aqueous NaOH (10%) was added, and the mixture was stirred for 15 min. The solution was cooled, diluted with water, and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by chromatography on silica gel (CH_2Cl_2/AcOEt, 9:1).

(7a*R*)-4-Acetyl-1,2,5,6,7,7a-hexahydropyrrolo[2,1,5-*cd*]indolizine (3a): IR (NaCl) 1657 (CO) cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ 1.24−1.28 (m, 1H, H-7), 1.72−1.77 (m, 1H, H-6), 1.94−1.98 (m, 1H, H-1), 2.10−2.18 (m, 1H, H-6), 2.18−2.20 (m, 1H, H-7), 2.35 (s, 3H, CH_3), 2.53−2.57 (m, 1H, H-1), 2.70−2.79 (m, 2H, H-2), 2.79−2.83 (m, 1H, H-5), 3.10−3.17 (m, 1H, H-5), 3.81−3.87 (m, 1H, H-7a), 6.17 (s, 1H, H-3); ^{13}C NMR (75 MHz; $CDCl_3$) δ 20.1 (C-6), 21.8 (C-5), 23.1 (C-2), 25.2 (CH_3), 27.8 (C-7), 35.8 (C-1), 54.0(C-7a), 101.1 (C-3), 121.2 (C-4), 137.8, 149.9, 194.6 (CO); MS (CI) 190 ($MH^{\cdot+}$).

Structure Determination of 3a. Apart from the signals corresponding to the aromatic protons at δ = 6.17 and 6.19 ppm, the one-dimensional ^{1}H NMR spectrum of compounds **3** showed overlapping signals of aliphatic protons. According to the integral values, the chemical shift of the aromatic proton of the major regioisomer was δ = 6.17 ppm. To determine the structure of **3a**, several two-dimensional NMR experiments were envisaged. In a (^{1}H, ^{1}H) COSY experiment, we started from the characteristic position of the H-7a atom (δ = 3.81−3.87 ppm) to establish the chemical shifts of all aliphatic protons. The obtained results were confirmed by NOE experiments. In a next step, GHMQC signals of H-2/C-2 allowed us to determined the C-2 chemical shift at δ = 23.1 ppm. Finally, GHMBC experiments displayed a long-range correlation between the C-2 and H-3 at δ = 6.17 ppm. All these results were in good agreement with the proposed structure. The structure of the other obtained regioisomers was determined in a similar way.

(7a*R*)-3-Acetyl-1,2,5,6,7,7a-hexahydropyrrolo[2,1,5-*cd*]indolizine (3b): IR (NaCl) 1657 (CO) cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ 1.27−1.33 (m, 1H, H-7), 1.76−1.79 (m, 1H, H-6), 1.87−1.89 (m, 1H, H-6), 2.16−2.19 (m, 1H, H-1), 2.18−2.21 (m, 1H, H-7), 2.35 (s, 3H, CH_3), 2.57−2.59 (m, 1H, H-5), 2.60−2.62 (m, 2H, H-1), 2.70−2.72 (m, 1H, H-5), 2.84−3.45 (m, 1H, H-2), 3.86−3.89 (m, 1H, H-7a), 6.19 (s, 1H, H-4); ^{13}C NMR (75 MHz; $CDCl_3$) δ 20.1 (C-6), 21.6 (C-5), 23.1 (C-2), 25.1 (CH_3), 27.8 (C-7), 35.6 (C-1), 54.1(C-7a), 105.3 (C-3), 116.1 (C-4), 121.2,131.6, 194.2 (CO).

(7a*R*)-4-Formyl-1,2,5,6,7,7a-hexahydropyrrolo[2,1,5-*cd*]-indolizine (6a): $[\alpha]^{20}_D$ = +99.4 (*c* 0.50, CH_2Cl_2); IR (NaCl) 1657

(CO) cm^{-1}; ^1H NMR (500 MHz; C_6D_6) δ 1.24−1.32 (m, 1H, H-7), 1.68−1.85 (m, 1H, H-6), 1.96−2.06 (m, 1H, H-1), 2.07−2.12 (m, 1H, H-6), 2.12−2.22 (m, 1H, H-7), 2.56−2.63 (m, 1H, H-1), 2.75−2.87 (m, 2H, H-2), 2.87−2.93 (m, 1H, H-5), 3.16−3.19 (m, 1H, H-5), 3.82−3.90 (m, 1H, H-7a), 6.21 (s, 1H, H-3), 9.67 (s, 1H, CHO); ^{13}C NMR (75 MHz; $CDCl_3$) δ 20.1 (C-6), 21.2 (C-5), 24.5 (C-2), 28.8 (C-7), 37.1 (C-1), 54.7 (C-7a), 101.6 (C-3), 125.2 (C-4), 132.1, 133.4, 184.0 (CO); MS (CI) 176 ($MH^{\cdot+}$). Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.40; N, 7.99. Found: C, 75.24; H, 7.37; N, 7.98.

(7a*R*)-3,4-Diformyl-1,2,5,6,7,7a-hexahydropyrrolo[2,1,5-*cd*]indolizine (6c): $[\alpha]^{20}_D = +108.8$ (*c* 0.25, CH_2Cl_2); IR (NaCl) 1665 (CO) cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 1.26−1.41 (m, 1H, H-7), 1.86−1.92 (m, 1H, H-6), 2.09−2.13 (m, 1H, H-1), 2.13−2.19 (m, 1H, H-6), 2.19−2.28 (m, 1H, H-7), 2.68−2.74 (m, 1H, H-1), 2.74−2.88 (m, 2H, H-2), 2.88−3.11 (m, 2H, H-5), 3.91−4.07 (m, 1H, H-7a), 10.11 (s, 1H, CHO), 10.03 (s, 1H, CHO); ^{13}C NMR (75 MHz; $CDCl_3$) δ 20.0 (C-6), 21.6 (C-2), 25.1 (C-5), 28.6 (C-7), 36.5 (C-1), 55.9 (C-7a), 117.9, 121.9, 135.1, 142.9, 185.8 (CO); 186.4 (CO); MS (CI) 204 ($MH^{\cdot+}$). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.66; H, 6.55; N, 6.93.

(7a*R*)-1,2,5,6,7,7a-Hexahydro-4-propionylpyrrolo[2,1,5-*cd*]indolizine (7a): IR (NaCl) 1646 (CO) cm^{-1}; ^1H NMR (500 MHz; $CDCl_3$) δ 1.16 (t, J = 7.5 Hz, 3H, CH_3), 1.21−1.37 (m, 1H, H-7), 1.69−1.80 (m, 1H, H-6), 1.87−2.01 (m, 1H, H-1), 2.09−2.20 (m, 2H, H-6 and H-7), 2.54−2.60 (m, 1H, H-1), 2.66 (q, 2H, CH_2), 2.67−2.77 (m, 1H, H-2), 2.77−2.83 (m, 2H, H-3), 2.83−2.87 (m, 1H, H-5), 3.09−3.22 (m, 1H, H-5), 3.66−3.85 (m, 1H, H-7a), 6.18 (s, 1H, H-3); ^{13}C NMR (75 MHz; $CDCl_3$) δ (ppm) 21.3 (C-6), 23.0 (C-5), 24.4 (C-2), 28.8 (C-7), 32.7 (CH_2), 37.6 (C-1), 55.2 (C-7a), 101.0 (C-3), 118.0 (C-1), 122.6, 130.7, 197.1 (CO); MS (CI) 204 ($MH^{\cdot+}$). This compound was obtained as a mixture with its isomer **7b** (see Table 1). **7b** was characterized by its H-2 chemical shift at δ = 6.21 ppm.

(7a*R*)-4-(3-Methylpropionyl)-1,2,5,6,7,7a-hexahydropyrrolo[2,1,5-*cd*]indolizine (8a): IR (NaCl) 1648 (CO) cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 1.48 (d, J = 2.7 Hz, 3H, CH_3), 1.50 (d, J = 2.7 Hz, 3H, CH_3), 1.65−1.78 (m, 1H, H-7), 1.73−1.80 (m, 1H, H-6), 2.01−2.11 (m, 1H, H-1), 2.11−2.22 (m, 2H, H-7 and H-6), 2.56−2.63 (m, 1H, H-1), 2.75−2.99 (m, 3H, 2H-2 and $CH(CH_3)_2$), 3.09−3.21 (m, 2H, H-5), 3.82−3.94 (m, 1H, H-7a), 6.20 (s, 1H, H-3); ^{13}C NMR (75 MHz; $CDCl_3$) δ 19.3 (CH_3), 19.5 (CH_3), 21.4 (C-6), 23.1 (C-5), 24.5 (C-2), 26.7 (C-7), 29.3 (C-1), 37.1 (CH), 55.4 (C-7a), 101.2 (C-3), 119.6 (C-4), 132.2, 138.1, 200.3 (CO); MS (CI) 218 ($MH^{\cdot+}$). This compound was obtained as a mixture with its isomer **8b** (see Table 1). **8b** was characterized by its H-3 chemical shift at δ = 6.23 ppm.

(7a*R*)-4-Ethyl-1,2,5,6,7,7a-hexahydropyrrolo[2,1,5-*cd*]indolizine (10). A 1 M solution of methyllithium in diethyl ether (0.270 mL, 0.43 mmol) was added at 0 °C to a solution of aldehyde **6a** (0.50 g, 0.39 mmol) in THF (5 mL). The resulting mixture was stirred under N_2 at 0 °C for 30 min and at room temperature for 30 min. THF was then evaporated, and the crude product was dissolved in 1,4-dioxane (5 mL). A suspension of $AlLiH_4$ (0.70 g, 1.74 mmol) in dioxane (5 mL) was carefully added. The solution was then stirred at 88 °C for 3 h, cooled at 0 °C, and quenched slowly with a saturated aqueous Na_2SO_4 solution. After filtration, the organic layer was dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (pentane/CH_2Cl_2, 9/1) of the residue gave pure compound **10** (yield: 72%). The obtained ^1H and ^{13}C NMR spectra were in agreement with those in the litterature.[3]

(7a*R*)-4-Ethyl-3-formyl-1,2,5,6,7,7a-hexahydropyrrolo-[2,1,5-*cd*]indolizine (11). The experimental procedure was similar to the one reported for the formylation of **1**: yield 80%; $[\alpha]^{20}_D = +94.2$ (*c* 0.5, CH_2Cl_2); IR (NaCl) 1665 (CO) cm^{-1}; ^1H NMR (300 MHz; $CDCl_3$) δ 1.24 (t, J = 4.8 Hz, 3H, CH_3), 1.27−1.38 (m, 1H, H-7), 1.69−1.84 (m, 1H, H-6), 1.93−2.10 (m, 1H, H-1), 2.12−2.21 (m, 2H, H-7 and H-6), 2.40−2.89 (m, 5H, H-1, 2H-5, CH_2), 2.92−3.06 (m, 2H, H-2), 3.78−3.80 (m, 1H, H-7a), 9.74 (s, 1H, CHO); ^{13}C NMR (75 MHz; $CDCl_3$) δ 15.6 (CH_3), 18.3 (CH_2), 19.4 (C-5), 22.1 (C-6), 24.3 (C-2), 29.2 (C-7), 36.3 (C-1), 56.0 (C-7a), 116.6, 121.3, 123.9, 141.5, 184.4 (CO). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.79; H, 8.46; N, 6.88.

(7a*R*)-4-Ethyl-1,2,5,6,7,7a-hexahydro-3-propenylpyrrolo-[2,1,5-*cd*]indolizine M215A/B. NaH (1.07 mmol) was added to a solution of (ethyl)triphenylphosphonium bromide (0.4 g,1.07 mmol) in THF (5 mL). A solution of aldehyde **11** (0.128 g, 0.63 mmol) in THF (5 mL) was then carefully added, and the resulting mixture was refluxed for 12 h. The reaction was quenched with water. The organic layer was dried ($MgSO_4$) and evaporated. Column chromatography on silica gel (CH_2Cl_2) of the residue gave M215 A/B (4/1) (yield: 78%). The obtained ^1H and ^{13}C NMR spectra were in agreement with those in the litterature.[1]

Supporting Information Available: NMR spectra of obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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