Intramolecular Cycloadditions of Nitrones Derived from 1-Allyl-2-pyrrolecarbaldehyde as a Route to Racemic and Enantiopure Pyrrolizidines and Indolizidines

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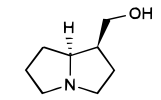
A version of the intramolecular nitrone cycloaddition strategy, using 2-pyrrolecarbaldehyde as starting material, has been developed to synthesize new pyrrolizidines and indolizidines structurally related to biologically active alkaloids. The target molecules have been accessible in racemic as well as enantiopure form.

Introduction

Pyrrolizidine and indolizidine alkaloids are endowed with a vaste range of potent biological activities.[1] Several of them (e.g., isoretronecanol (**1**), petasinecine (**2**), swainsonine (**3**), and castanospermine (**4**)) have been proven glycosidase inhibitors and constitute promising antiviral and antitumoral agents.[2]



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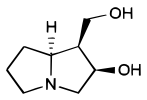

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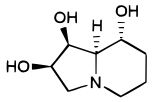

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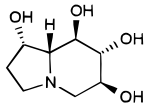

(+) - **4**

In view of these features as well as of the exotic provenance and the scarsity of natural samples, there is a great impulse toward the synthesis of such alkaloids and structurally related unnatural compounds.[3] To attain this goal, various authors have employed cycloaddition reactions of nitrone intermediates.[4] Two intramolecular versions of the same strategy, which could be in principle more efficient in terms of stereoselectivity, are also known: the first one is directed to the synthesis of indolizidines and uses (*S*)-5-(hydroxymethyl)-2-pyrrolidone as primary chiral material;[5] the second one deals with a synthetic entry to pyrrolizidines starting from (*S*)-proline.[6]

The present paper describes a new approach to the pyrrolizidine and indolizidine skeletons, essentially based upon the intramolecular cycloaddition of nitrones derived from 1-allyl-2-pyrrolecarbaldehyde (**5**) (Scheme 1). Although the reactivity of similar nitrones has been investigated,[7] its potential in alkaloid synthesis has not been exploited. In addition, other authors have turned their attention to the behavior of nitrones derived from 1-allyl-2-indolecarbaldehyde.[8]

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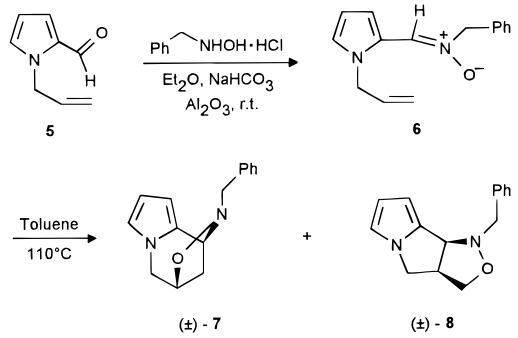
Scheme 1



Results and Discussion

(A) Synthesis of Racemic Compounds. The reaction of aldehyde **5** with the commercially available benzylhydroxylamine gave the desired nitrone **6** in 52% yield. Heating the latter in refluxing toluene led to the isomeric cycloadducts **7** and **8** in 57 and 34% yields, respectively.[9] Both ^{1}H and ^{13}C NMR spectra showed that compound **7** exists as a 4:1 mixture of two invertomers, in agreement with literature precedents for encumbered *N*-substituted isoxazolidines.[10] The observed coalescence temperature (28 °C) corresponds to an inversion energy barrier of ca. 15 kcal/mol.[11] MM+ calculations[12] have shown the invertomer having the benzyl group in pseudoaxial position more stable by 1.3 kcal/mol in comparison with that having the same pendant in pseudoequatorial position.

The behavior of nitrone **6** deserves a few comments. The isomeric products **7** and **8** reflect two opposite regiochemical trends of the cycloaddition, both of which however give exclusively a cis relationship of the new stereocenters. The latter outcome is clearly the consequence of geometric restraints and constitutes an intrinsic advantage of intramolecular nitrone cycloadditions with respect to the intermolecular ones. The predominance of the bridged-ring product **7** is worthy of noting because only fused-ring products have been found in the intramolecular cycloaddition of nitrones derived from *N*-alkenyl-2-prolinaldehyde.[6c,d] It may be that, because of the rigid angular disposition imparted by the planar pyrrole nucleus, the fused-ring transition state increases in energy thereby becoming competitive with the usually unfavored bridged-ring transition state (Figure 1). As molecular models indicate, this is not the case for the more flexible pyrrolidine nucleus of proline. MM+ calculations, assuming a distance of 2.7 Å between the reaction centers, have estimated the transition state **B** higher in energy of 0.8 kcal/mol with respect to **A**. Significantly, in the case of the analogous structures containing a pyrrolidine ring, the same computational approach has indicated an energy difference of 16.5 kcal/mol in favor of the fused-ring transition state of type **B**.

At this point, we submitted the above cycloadducts **7** and **8** to hydrogenolytic treatment with the idea of (i) removing the benzyl group, (ii) opening the isoxazolidine ring, and (iii) saturating the pyrrole nucleus. Preliminary experiments showed a marked influence by both the catalyst and the reaction conditions. Upon hydrogenation in methanol in the presence of 10% Pd/C at rt and 15 psi of pressure, compound **7** gave after 6 h the amino alcohol **9** and the alcohol **10** in 12 and 50% yields, respectively (Scheme 2). The loss of the primary amino group, although rather disappointing, is not unespected due to its pseudobenzylic position. However, when the hydrogenolytic treatment of **7** was prolonged until 48 h, we isolated the isomeric 6-hydroxyindolizidines **13** (25%) and **14** (22%).[13] Compound **8** was found more reluctant toward hydrogenation. Under the conditions indicated above, it gave after 24 h the amino alcohol **12** as the only product, the species **11** being isolable at short time (3 h). Saturation of the pyrrole nucleus proceeded slowly and partially under these conditions, but it was facilitated by the additional presence of hydrogen chloride, which allowed the obtainment of 2-hydroxypyrrolizidine (**15**) in 51% yield.[14]

Structural assignments to the fully hydrogenated products required homonuclear and heteronuclear shift correlations. Significantly, the bridgehead hydrogen resonates at 3.57 ppm in **15**, in accord with the cis

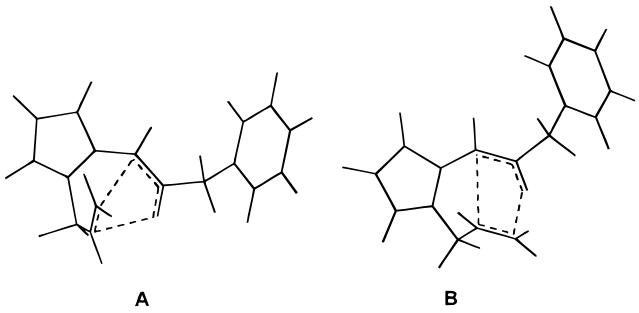
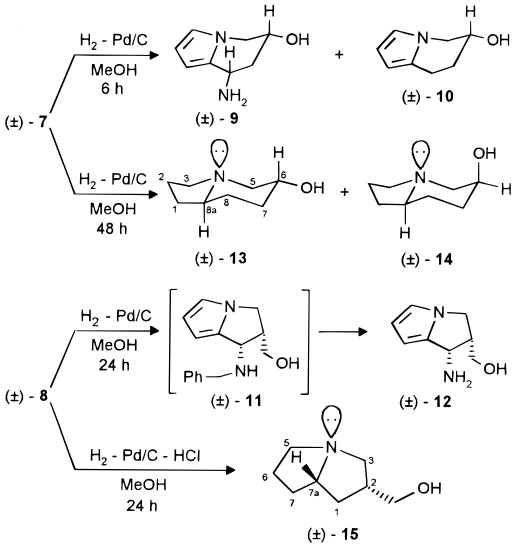


Figure 1. Bridged-ring (**A**) and fused-ring (**B**) transition states for the intramolecular cycloaddition of nitrone **6**.

Scheme 2



(9) When the reaction of **5** with benzylhydroxylamine was carried out at high temperature, compounds **7** and **8** could be obtained without isolating the intermediate nitrone **6**. However, the overall yields were less satisfactory.

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(12) HyperChem program (4.1 version, Autodesck, Inc.).

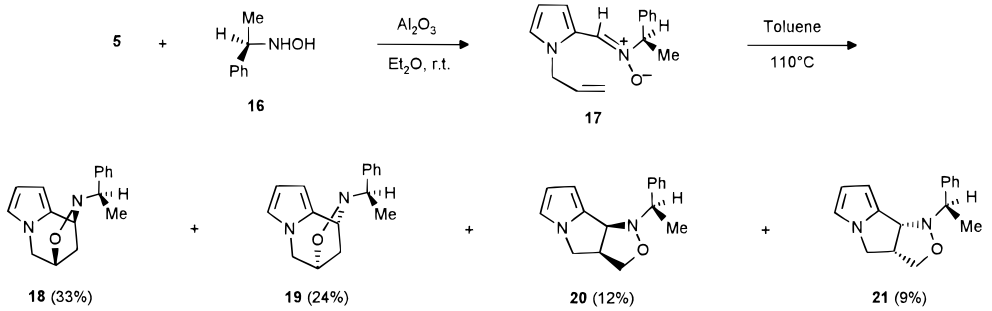
(13) No improved result was observed by using $Pd(OH)_2$ as catalyst.

(14) Attempts to isolate **13**−**15** as hydrochlorides gave highly hygroscopic solids difficult to handle and to characterize. The saturation of the pyrrole nucleus of **8** was also observed, without the presence of hydrogen chloride, using acetic acid as solvent. However, under these conditions, the isolation of the product suffered from a drawback due to the combination of its basicity and volatility.

Table 1. Selected Connectivities Established by NOE Difference Studies

proton irradiated	protons affected (%) in compound	
	18	**19**
Me	H_C(3.5), H_I(4), H_L(7.5), Ph(2.5)	H_C(<0.5), H_I(<0.5), H_L(7), Ph(2)
Ph	H_C(<0.5), H_I(1.5), H_L(8), Me(1)	H_C(4), H_I(2.5), H_L(8), Me(1)
H_L	H_C(0.5), H_I(1.5), H_G(3), Me(1,5), Ph(4.5)	H_C(1), H_I(1), H_C(<0.5), Me(2), Ph(4.5)
H_C	H_I(2.5), H_L(0.5), Me(0.5)	H_I(2), H_L(1), Ph(2)
H_G	H_F(4.5), H_H(20), H_I(3.5), H_L(3)	H_F(4.5), H_H(18), H_I(3), H_L(<0.5)

Scheme 3



junction of the rings, and at less than 1.90 ppm in **13** and **14**, thus indicating in both isomers a diaxial trans disposition with respect to the lone electron pair on the nitrogen. The distinction between the diastereoisomers **13** and **14** was possible because H-6 shows two coupling constants of 10.1 Hz typical of trans diaxial interactions in compound **13**, while it exhibits four vicinal couplings of ca. 2.4 Hz indicating its equatorial disposition in compound **14**. On the other hand, in the case of **15**, the 1,3-syn relationship between H-2 and H-7a was established unequivocally by 2D NOE measurements.[15]

(B) Synthesis of Enantiopure Compounds. The second part of this paper is concerned with the asymmetric synthesis of the new pyrrolizidines and indolizidines just described in the first part. As a device aimed at this goal, we ideated the use of an enantiopure hydroxylamine and chose (*R*)-*N*-(1-phenylethyl)hydroxylamine (**16**) in view of its benzylic nature as well as of its ready accessibility.[16] Actually, the reaction of aldehyde **5** with **16** gave the optically active nitrone **17** in 48% yield (Scheme 3). Heat treatment of the latter resulted in a mixture of four products, all of which were obtained in pure state by means of column chromatography. Analytical and spectral data were consistent with two diastereoisomeric bridged-ring cycloadducts and two diastereoisomeric fused-ring cycloadducts. The proportion between the two types of structures (ca. 2:1) is rather similar to that found in the intramolecular cycloaddition of *N*-benzylnitrone (**6**). Within each diastereoisomeric pair, the observed ratio (ca. 4:3) corresponds to a moderate asymmetric induction by the homochiral pendant. It is to be added that the major bridged-ring cycloadduct exists as a 3:2 mixture of two invertomers with a coalescence temperature of 35 °C. Conversely, the minor bridged-ring cycloadduct exists as one largely predominant invertomer (10:1).

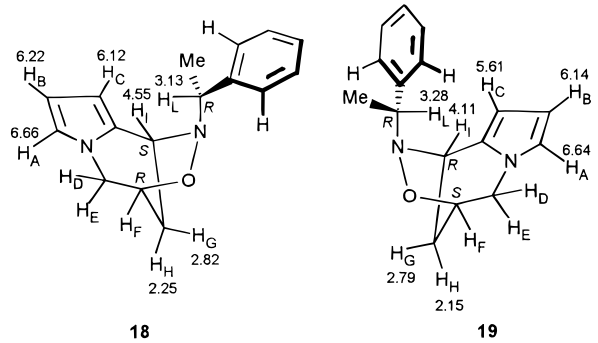


Figure 2. Preferred conformations and absolute configurations of the diastereoisomeric cycloadducts **18** and **19**.

The absolute stereochemistry of the diastereoisomeric bridged-ring cycloadducts **18** and **19** was elucidated by ^{1}H NMR. Observed NOE enhancements (Figure 2, Table 1) are consistent if (i) the *N*-pendant assumes preferably a pseudoaxial conformation with the smallest substituent at the benzylic carbon (i.e., H_L) oriented toward the inner concavity of the molecule and (ii) the newly formed stereocenters possess the absolute configurations depicted in the formulas. This conclusion agrees with the marked shielding effect exerted by the Ph ring on H_C in compound **19**, but not in compound **18**. Sizable mutual NOEs between H_L and H_G were also observed in compound **18** because of the rapid conversion to the minor invertomer having the *N*-pendant positionated pseudoequatorially; the corresponding NOEs were smaller in compound **19** according to the negligeable extent of the minor invertomer. MM+ calculations have shown that, on assuming the absolute configurations of **18**, the *N*-invertomer having the pendant disposed pseudoaxially is preferred of only 0.6 kcal/mol with respect to that having the pendant disposed pseudoequatorially. Conversely, on assuming the absolute configuration of **19**, the energy difference between pseudoaxial and pseudoequatorial dispositions rises to 3.4 kcal/mol in favor of the former one.

In the case of the diastereoisomeric fused-ring cycloadducts **20** and **21** (Figure 3), NOE enhancements between H_F and H_I (2%) clearly demonstrates their cis relationship. Moreover, in compound **20** the presence of NOE

(15) For previous NMR studies of pyrrolizidines and indolizidines see refs 4b, 5c, 6b, 6d, and the following: (a) Jones, T. H.; Blum, M. S.; Fales, H. M.; Thompson, C. R. *J. Org. Chem.* **1980**, *45*, 4778. (b) Belmont, S. E.; Polniaszek, R. P. *J. Org. Chem.* **1990**, *55*, 4688. (c) Bond, T. J.; Jenkins, R.; Ridley, A. C.; Taylor, P. C. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2241. (d) Logie, C. G.; Grue, M. R.; Liddell, J. R. *Phytochemistry* **1994**, *37*, 43.

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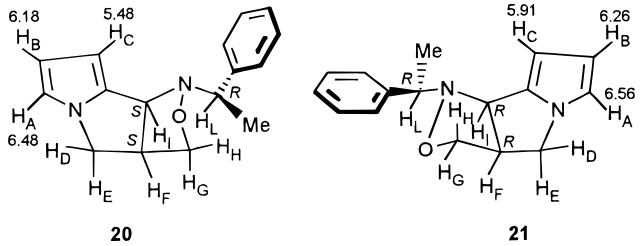

Figure 3. Preferred conformations and absolute configurations of the diastereoisomeric cycloadducts **20** and **21**.

Scheme 4[a]

18 —(a)→ (+)-(6*R*)-**10** ; **18** —(c)→ (+)-(6*R*,8a*R*)-**13** + (+)-(6*R*,8a*S*)-**14**

19 —(a)→ (-)-(6*S*)-**10** ; **19** —(c)→ (-)-(6*S*,8a*R*)-**13** + (-)-(6*S*,8a*S*)-**14**

20 —(b)→ (+)-(1*S*,2*S*)-**12** ; **20** —(d)→ (+)-(2*R*,7a*S*)-**15**

21 —(b)→ (-)-(1*R*,2*R*)-**12** ; **21** —(d)→ (-)-(2*S*,7a*R*)-**15**

[a] Key: (*a*) H_2 Pd/C, MeOH, 6 h; (*b*) H_2 Pd/C, MeOH, 24 h; (*c*) H_2 Pd/C, MeOH, 48 h; (*d*) H_2 Pd/C HCl, MeOH, 24 h.

(1%) between the Me protons and H_G as well as the shielding effect exerted by the facing Ph on H_C are only compatible with the (*S*,*S*) stereochemistry.

At the final stage of our work, we submitted the optically active cycloadducts **18**−**21** to catalytic hydrogenation, following the conditions adopted in the case of the analogous *N*-benzyl derivatives **7** and **8**. In this way, both enantiomers of compounds **10** and **12**−**15** became available (Scheme 4). The enantiomeric purity was determined in a few cases, namely (+)-**13** and (−)-**13**, upon functionalization by (+)-(2*R*,3*R*)-dibenzoyltartaric anhydride and subsequent NMR analysis at 300 MHz of the resulting monoester. It was proven to be total within the experimental error limits (>98%).

Conclusions

In summary, we have shown that nitrones derived from 1-allyl-2-pyrrolcarbaldehyde are useful intermediates for a valuable synthesis of pyrrolizidines and indolizidines structurally related to bioactive alkaloids. The accessibility of both racemic and enantiopure molecules must be emphasized. However, in addition to the already acquired goals, developments and improvements can be devised. The first one is the synthesis of more functionalized structures, which could be plausibly obtained from substrates having appropriate substituents at the pyrrole ring and/or at the allylic moiety. The second point is concerned with a better degree of asymmetric induction, which may hopefully be achieved by using a homochiral sugar-derived hydroxylamine. Work is in progress in both of these directions.

Experimental Section

Melting points are not corrected. Analytical and spectroscopic instruments were as described in detail in a recent paper.[17]

Compounds **5**[7] and **16**[16] were prepared according to the literature methods.

***N*-[(1-Allylpyrrol-2-yl)methylidene]benzenemethanamine *N*-Oxide (6).** A suspension of *N*-benzylhydroxylamine hydrochloride (3.0 g, 18.8 mmol), Al_2O_3 (30.0 g), and $NaHCO_3$ (2.1 g, 25 mmol) in Et_2O (150 mL) was stirred at room temperature for 1 h. A solution of **5** (2.1 g, 15.5 mmol) in Et_2O (100 mL) was added, and the resulting mixture was stirred for 24 h. After filtration and evaporation of the solvent under reduced pressure, the residue was chromatographed on a silica gel column with AcOEt as eluent to give 1.9 g (52%) of **6**. For **6**: mp 108−109 °C (from hexane/benzene); ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 4.43 (br d, J = 5.0 Hz, 2H), 4.79 (dd, J = 1.2, 17.1 Hz, 1H), 5.00 (s, 2H), 5.09 (dd, J = 1.2, 10.3 Hz, 1H), 5.80 (ddt, J = 4.9, 10.3, 17.1, 1H), 6.26 (dd, J = 2.7, 3.6 Hz, 1H), 6.76 (dd, J = 1.3, 2.7 Hz, 1H), 7.21 (s, 1H), 7.36−7.43 (m, 5H), 7.82 (dd, J = 1.3, 3.6 Hz, 1H); MS *m*/*z* 240 (M^+). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.96; H, 6.72; N, 11.66. Found: C, 75.03; H, 6.61; N, 11.74.

Intramolecular Cycloaddition of Nitrone 6. A solution of **6** (1.7 g, 7.1 mmol) in toluene (150 mL) was refluxed for 24 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel column with AcOEt−light petroleum (1:1) as eluent. The first fractions gave 0.58 g (34%) of (3a*R**,8b*R**)-1-benzyl-1,3a,4,8b-tetrahydro-3*H*-isoxazolo[3,4-*a*]pyrrolizine (**8**) as an oil: ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 3.85 (dd, J = 4.0, 8.3 Hz, 1H), 3.88−3.95 (m, 1H), 3.98 (dd, J = 3.3, 10.6 Hz, 1H), 4.03 and 4.12 (AB, J = 13.3 Hz, 2H), 4.16 (dd, J = 8.0, 10.6 Hz, 1H), 4.27 (br s, 1H), 4.50 (br s, 1H), 5.71−5.81 (m, 1H), 6.21−6.25 (m, 1H), 6.54−6.58 (m, 1H), 7.25−7.45 (m, 5H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 50.9 (d), 51.0 (t), 60.3 (t), 67.7 (d), 72.5 (t), 101.3 (d), 113.5 (d), 114.3 (d), 127.4 (s), 127.4 (d), 128.3 (d), 129.1 (d), 137.1 (s); MS *m*/*z* 240 (M^+). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.96; H, 6.72; N, 11.66. Found: C, 74.89; H, 6.63; N, 11.55. The last fractions contained 0.97 g (57%) of (1*R**,4*S**)-2-benzyl-1,2,4,5-tetrahydro-1,4-methanopyrrolo[2,1-*d*][1,2,5] oxadiazepine (**7**) isolated as an oil: ^{1}H NMR (δ, $CDCl_3$, 300 MHz) {*major conformer*} 2.25 (d, J = 10.9 Hz, 1H), 2.80 (ddd, J = 4.5, 6.6, 10.9 Hz, 1H), 3.53 and 3.58 (AB, J = 13.2 Hz, 2H), 4.00 (d, J = 12.5 Hz, 1H), 4.13 (d, J = 12.5 Hz, 1H), 4.29 (d, J = 4.5 Hz, 1H), 4.76 (br d, J = 6.6 Hz, 1H), 5.94−6.00 (m, 1H), 6.15−6.21 (m, 1H), 6.63−6.69 (m, 1H), 7.20−7.41 (m, 5H), {*minor conformer*} 2.17−2.23 (m, 1H), 2.62−2.76 (m, 1H), 3.50−4.30 (overlapping, 5H), 4.90−4.98 (m, 1H), 5.79−5.84 (m, 1H), 6.02−6.13 (m, 1H), 6.44−6.57 (m, 1H), 7.20−7.41 (m, 5H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) {*major conformer*} 36.5 (t), 53.3 (t), 56.3 (d), 59.1 (t), 72.7 (d), 106.9 (d), 108.0 (d), 119.9 (d), 127.1 (d), 127.4 (s), 128.3 (d), 129.0 (d), 137.6 (s) {*minor conformer*} 32.1 (t), 52.4 (t), 56.7 (d), 63.0 (t), 73.8 (d), 103.2 (d), 108.3 (d), 119.4 (d), 127.2 (d), 127.4 (s), 128.3 (d), 129.0 (d), 137.1 (s); MS *m*/*z* 240 (M^+). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.96; H, 6.72; N, 11.66. Found: C, 75.05; H, 6.84; N, 11.81.

Hydrogenation of 7 for 6 h. Pd/C (10%, 0.31 g, 0.3 mmol) was added to a solution of **7** (0.36 g, 1.5 mmol) in MeOH (40 mL). The mixture was stirred under H_2 for 6 h. After filtration through Celite, the solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel column. Elution with $CHCl_3$/MeOH (19:1) gave 0.10 g (50%) of 6-hydroxy-5,6,7,8-tetrahydroindolizidine (**10**) as an oil: ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 1.75 (br s, 1H, missing after deuteriation), 1.90 (dddd, J = 6.0, 7.1, 7.9, 13.3 Hz, 1H), 2.04 (dddd, J = 2.7, 6.0, 7.0, 13.3 Hz, 1H), 2.79 (ddd, J = 6.0, 7.9, 16.4 Hz, 1H), 2.96 (ddd, J = 6.0, 7.0, 16.4 Hz, 1H), 3.81 (dd, J = 6.4, 12.0 Hz, 1H), 4.11 (dd, J = 4.2, 12.0 Hz, 1H), 4.21−4.30 (m, 1H), 5.85 (dd, J = 1.5, 3.5 Hz, 1H), 6.14 (dd, J = 2.5, 3.5 Hz, 1H), 6.50 (dd, J = 1.5, 2.5 Hz, 1H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 19.4 (t), 29.3 (t), 51.6 (t), 65.7 (d), 104.1 (d), 108.4 (d), 118.8 (d), 127.7 (s); IR (Nujol) 3380 cm^{-1}; MS *m*/*z* 137 (M^+). Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.95; H, 8.01; N, 10.15. Subsequent elution with $CHCl_3$/MeOH/30% NH_3 (10:1:1) gave 0.027 g (12%) of (6*R**,8*S**)-8-amino-6-hydroxy-5,6,7,8-tetrahydroindolizine (**9**) as an oil: ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 1.90 (ddd, J = 3.0, 3.1, 14.0 Hz, 1H), 2.14 (ddd, J = 2.9, 3.4, 14.0 Hz, 1H), 2.33 (br s, 3H, missing after deuteriation), 3.95 (dd, J = 3.2, 12.7 Hz, 1H), 4.22 (br d, J = 12.7 Hz, 1H), 4.38−4.41 (m, 1H), 4.55 (br dd, J = 3.1, 3.4 Hz, 1H), 6.06 (dd, J = 1.5, 3.5 Hz, 1H), 6.19 (dd, J = 2.5, 3.5 Hz, 1H), 6.59 (dd, J = 1.5, 2.5 Hz, 1H);^{13}C NMR (δ, $CDCl_3$, 75 MHz) 33.2 (t), 43.6 (d), 53.4 (t), 66.4 (d), 105.4 (d), 108.4 (d), 120.4 (d), 130.3 (s); IR (Nujol) 3240, 3290, 3350

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cm^{-1}; MS *m*/*z* 152 (M$^+$). Anal. Calcd for $C_8H_{12}N_2O$: C, 63.12; H, 7.95; N, 18.41. Found: C, 62.99; H, 7.84; N, 18.53.

Hydrogenation of 7 for 48 h. Pd/C (10%, 0.14 g, 0.13 mmol) was added to a solution of **7** (0.14 g, 0.58 mmol) in MeOH (25 mL). The mixture was stirred under H_2 for 48 h. After filtration through Celite, the solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel column with $CHCl_3$/MeOH (1:3) as eluent. The first fraction gave 0.020 g (25%) of (6*R**,8a*R**)-6-hydroxy-1,2,3,5,6,7,8,8a-octahydroindolizidine (**13**) as an oil: ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 1.20−1.40 (overlapping, 3H, H-1, H-7, H-8), 1.60−1.92 (overlapping, 6H, H-1, H-2, H-2, H-5ax, H-8, H-8a), 2.00−2.07 (m, 1H, H-7), 2.15 (dt, *J* = 8.7, 8.7 Hz, 1H, H-3), 2.38 (br s, 1H, O*H*, missing after deuteriation), 2.98 (dt, *J* = 1.7, 8.7 Hz, 1H, H-3), 3.24 (ddd, *J* = 1.5, 4.1, 10.1, 1H, H-5eq), 3.84 (tt, *J* = 4.1, 10.1 Hz, 1H, H-6);^{13}C NMR (δ, $CDCl_3$, 75 MHz) 22.2 (t, C-2), 29.1 (t, C-1 or C-8), 30.2 (t, C-1 or C-8), 34.6 (t, C-7), 54.3 (t, C-3), 60.6 (t, C-5), 64.3 (d, C-8a), 68.3 (d, C-6); IR (Nujol) 3360 cm^{-1}; MS *m*/*z* 141 (M$^+$). Anal. Calcd for $C_8H_{15}NO$: C, 68.03; H, 10.71; N, 9.92. Found: C, 68.08; H, 10.59; N, 9.99. The next fraction gave 0.018 g (22%) of (6*R**,8a*S**)-6-hydroxy-1,2,3,5,6,7,8,8a-octahydroindolizine (**14**) as an oil: ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 1.30−1.91 (overlapping, 9H, H-1, H-1, H-2, H-2, H-7, H-7, H-8, H-8, H-8a), 2.09 (dt, *J* = 9.1, 9.1 Hz, H-3), 2.15 (dd, *J* = 2.4, 11.2 Hz, 1H, H-5ax), 2.40 (br s, 1H, O*H*, missing after deuteriation), 2.97 (dt, *J* = 2.4, 9.1 Hz, 1H, H-3), 3.07 (ddd, *J* = 2.3, 2.4, 11.2 Hz, H-5eq), 3.88 (br quintet, *J* = 2.4 Hz, 1H, H-6); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 21.4 (t, C-2), 26.4 (t, C-1 or C-8), 31.1 (t, C-1 or C-8), 31.6 (t, C-7), 54.6 (t, C-3), 59.4 (t, C-5), 64.8 (d, C-8a), 66.0 (d, C-6); IR (Nujol) 3360 cm^{-1}; MS *m*/*z* 141 (M$^+$). Anal. Calcd for $C_8H_{15}NO$: C, 68.03; H, 10.71; N, 9.92. Found: C, 67.89; H, 10.61; N, 10.04.

Hydrogenation of 8 without HCl. Pd/C (10%, 0.11 g, 0.1 mmol) was added to a solution of **8** (0.12 g, 0.5 mmol) in MeOH (18 mL). The mixture was stirred under H_2 for 24 h. After filtration through Celite, the solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel column with $CHCl_3$/MeOH (19:1) as eluent to obtain 0.052 g (68%) of (1*R**,2*R**)-1-amino-2,3-dihydro-1*H*-pyrrolizine-2-methanol (**12**) as an oil: ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 2.55 (br s, 3H, missing after deuteriation), 3.05 (dddt, *J* = 3.6, 7.0, 7.4, 7.6 Hz, 1H), 3.85 (dd, *J* = 7.0, 11.8 Hz, 1H), 3.95 (dd, *J* = 3.6, 11.8 Hz, 1H), 3.98 (d, *J* = 7.6, 2H), 4.56 (d, *J* = 7.4 Hz, 1H), 5.90 (dd, *J* = 1.1, 3.5 Hz, 1H), 6.23 (dd, *J* = 2.5, 3.5 Hz, 1H), 6.58 (dd, *J* = 1.1, 2.5 Hz, 1H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 47.3 (t), 47.8 (d), 51.5 (d), 62.5 (t), 99.9 (d), 113.2 (d), 115.1 (d), 140.8 (s); IR (Nujol) 3175, 3280, 3350 cm^{-1}; MS *m*/*z* 152 (M$^+$). Anal. Calcd for $C_8H_{12}N_2O$: C, 63.12; H, 7.95; N, 18.41. Found: C, 63.08; H, 8.02; N, 18.49.

When the hydrogenation was stopped after 3 h, (1*R**,2*R**)-1-(benzylamino)-2,3-dihydro-1*H*-pyrrolizine-2-methanol (**11**) was isolated in 20% yield as an oil: ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 1.92 (br s, 2H, missing after deuteriation), 3.08−3.22 (m, 1H), 3.84 (dd, *J* = 7.3, 11.9 Hz, 1H), 3.90 and 4.02 (AB, *J* = 12.9 Hz, 2H), 3.97 (dd, *J* = 4.1, 11.9 Hz, 1H), 3.97 (d, *J* = 8.2 Hz, 2H), 4.26 (d, *J* = 7.5 Hz, 1H), 5.96 (dd, *J* = 1.0, 3.5 Hz, 1H), 6.23 (dd, *J* = 2.5, 3.5 Hz, 1H), 6.61 (dd, *J* = 1.0, 2.5 Hz, 1H), 7.27−7.35 (m, 5H); IR (Nujol) 3250, 3280 cm^{-1}; MS *m*/*z* 242 (M$^+$). Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.34; H, 7.49; N, 11.57. Found: C, 74.40; H, 7.61; N, 11.48.

Hydrogenation of 8 in the Presence of HCl. Compound **8** (0.10 g, 0.42 mmol) was dissolved in a 0.04 N solution of HCl in MeOH (10 mL) and treated with 10% Pd/C (0.090 g, 0.084 mmol). The mixture was stirred under H_2 for 24 h. After filtration through Celite, the solvent was evaporated under reduced pressure. The residue was treated with 50% NaOH and extracted with CH_2Cl_2. After the evaporation of the solvent, the crude product was chromatographed on a silica gel column with CH_2Cl_2/MeOH/30% NH_3 (5:1:1) as eluent to obtain 0.030 g (51%) of (2*R**,7a*S**)-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine-2-methanol (**15**) as an oil: ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 1.12 (dt, *J* = 9.0, 12.0 Hz, 1H, H-1), 1.41−1.53 (m, 1H, H-7), 1.68−1.98 (overlapping, 4H, H-6, H-6, H-7, O*H*, 3H after deuteriation), 2.11 (dt, *J* = 6.3, 12.0 Hz, 1H, H-1), 2.24 (dd, *J* = 9.2, 10.5 Hz, 1H, H-3), 2.48 (ddddt, *J* = 6.1, 6.3, 6.4, 9.0, 10.5 Hz, 1H, H-2), 2.59 (dt, *J* = 6.2, 10.5 Hz, 1H, H-5), 2.96 (dt, *J* = 6.2, 10.5 Hz, 1H, H-5), 3.24 (dd, *J* = 6.4, 9.2 Hz, 1H, H-3), 3.57 (dddd, *J* = 6.3, 6.4, 9.0, 10.5 Hz, 1H, H-7a), 3.64 (d, *J* = 6.1 Hz, 2H, C*H*$_2$OH); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 25.7 (t, C-6), 32.3 (t, C-7), 36.1 (t, C-1), 44. 8 (d, C-2), 54.8 (t, C-5), 58.3 (t, C-3), 64.7 (t, *C*H$_2$OH), 65.8 (d, C-7a); IR (Nujol) 3380 cm^{-1}; MS *m*/*z* 141 (M$^+$). Anal. Calcd for $C_8H_{15}NO$: C, 68.03; H, 10.71; N, 9.92. Found: C, 67.90; H, 10.65; N, 9.81.

(*R*)-*N*-[(1-Allylpyrrol-2-yl)methylidene]-α-methylbenzenemethanamine *N*-Oxide (17). A suspension of **5** (1.50 g, 11.1 mmol), **16** (1.54 g, 11.2 mmol) and Al_2O_3 (15.0 g) in Et_2O (40 mL) was stirred at room temperature for 5 d. After filtration and evaporation of the solvent under reduced pressure, the residue was chromatographed on a silica gel column with AcOEt as eluent to give 1.36 g (48%) of **17**: mp 122−124 °C (from hexane/benzene); $[\alpha]_D^{25}$ = +12.5 (*c* = 0.18, $CHCl_3$); ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 1.88 (d, *J* = 6.6 Hz, 3H), 4.46 (br d, *J* = 4.9 Hz, 2H), 4.85 (br d, *J* = 17.1 Hz, 1H), 5.10 (q, *J* = 6.6 1H), 5.11 (br d, *J* = 10.3 Hz, 1H), 5.80 (ddt, *J* = 4.9, 10.3, 17.1 Hz, 1H), 6.26 (dd, *J* = 2.7, 3.6 Hz, 1H), 6.76 (dd, *J* = 1.3, 2.7 Hz, 1H), 7.31 (s, 1H), 7.35−7.49 (m, 5H), 7.82 (dd, *J* = 1.3, 3.6 Hz, 1H); MS *m*/*z* 254 (M$^+$). Anal. Calcd for: $C_{16}H_{18}N_2O$: C, 75.55; H, 7.14; N, 11.02. Found: C, 75.59; H, 7.05; N, 10.94.

Intramolecular Cycloaddition of Nitrone 17. A solution of **17** (0.96 g, 3.8 mmol) in toluene (70 mL) was refluxed for 24 h. The solvent was evaporated under reduced pressure, and the residue was chromatographed on a silica gel column with AcOEt/light petroleum (1:1) as eluent. The first fraction gave 0.086 g (9%) of (+)-(α*R*,3a*R*,8b*R*)-1-(α-phenylethyl)-1,-3a,4,8b-tetrahydro-3*H*-isoxazolo[3,4-*a*]pyrrolizine (**21**) as an oil: $[\alpha]_D$ = +48.9 (*c* = 0.190, $CHCl_3$); ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 1.51 (d, *J* = 6.6 Hz, 3H, Me), 3.74 (dd, *J* = 4.7, 8.2 Hz, 1H, H-3), 3.82 (ddddd, *J* = 3.5, 4.7, 7.3, 7.9, 8.1 Hz, 1H, H-3a), 3.94 (dd, *J* = 3.6, 10.6 Hz, 1H, H-4), 4.03 (q, *J* = 6.6 Hz, 1H, C*H*Me), 4.08 (dd, *J* = 8.1, 10.6 Hz, 1H, H-4), 4.14 (dd, *J* = 7.3, 8.2 Hz, 1H, H-3), 4.55 (d, *J* = 7.9 Hz, 1H, H-8b), 5.91 (dd, *J* = 1.4, 3.5 Hz, 1H, H-8), 6.26 (dd, *J* = 2.7, 3.5 Hz, 1H, H-7), 6.56 (dd, *J* = 1.4, 2.7 Hz, 1H, H-6), 7.22−7.45 (m, 5H, Ph);^{13}C NMR (δ, $CDCl_3$, 75 MHz) 22.0 (q), 50.2 (d), 50.7 (t), 63.9 (d), 66.1 (d), 71.7 (t), 101.0 (d), 113.7 (d), 113.9 (d), 127.4 (s), 127.5 (d), 127.8 (d), 128.5 (d), 143.2 (s); MS: *m*/*z* 254 (M$^+$). Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.55; H, 7.14; N, 11.02. Found: C, 75.45; H, 7.15; N, 10.91. The second fraction contained 0.12 g (12%) of (+)-(α*R*,3a*S*,8b*S*)-1-(α-phenylethyl)-1,3a,4,8b-tetrahydro-3*H*-isoxazolo[3,4-*a*]pyrrolizine (**20**) isolated as an oil: $[\alpha]_D$ = +10.3 (*c* = 0.18, $CHCl_3$);^{1}H NMR (δ, $CDCl_3$, 300 MHz) 1.50 (d, *J* = 6.3 Hz, 3H, Me), 3.80 (ddddd, *J* = 2.9, 3.0, 7.3, 7.8, 8.0 Hz, 1H, H-3a), 3.83 (dd, *J* = 3.0, 8.9 Hz, 1H, H-3), 3.93 (dd, *J* = 2.9, 10.6 Hz, 1H, H-4), 3.95 (q, *J* = 6.3 Hz, 1H, C*H*Me), 4.10 (dd, *J* = 7.8, 10.6 Hz, 1H, H-4), 4.22 (dd, *J* = 8.0, 8.9 Hz, 1H, H-3), 4.54 (d, *J* = 7.3 Hz, 1H, H-8b), 5.38−5.58 (m, 1H, H-8), 6.13−6.22 (m, 1H, H-7), 6.45−6.52 (m, 1H, H-6), 7.27−7.45 (m, 5H, Ph); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 21.9 (q), 50.0 (d), 50.8 (t), 63.7 (d), 66.1 (d), 71.5 (t), 100.7 (d), 113.4 (d), 113.7 (d), 127.4 (s), 127.4 (d), 127.6 (d), 128.4 (d), 143.0 (s); MS *m*/*z* 254 (M$^+$). Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.55; H, 7.14; N, 11.02. Found: C, 75.67; H, 7.26; N, 11.11. The third fraction gave 0.32 g (33%) of (+)-(α*R*,1*S*,4*R*)-2-(α-phenylethyl)-1,2,4,5-tetrahydro-1,4-methanopyrrolo[2,1-*d*][1,2,5]oxadiazepine (**18**) as an oil: $[\alpha]_D$ = +33.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (δ, $CDCl_3$, 300 MHz) {*major conformer*} 1.32 (d, *J* = 6.5 Hz, 3H, Me), 2.25 (br d, *J* = 11.0 Hz, 1H, H-10), 2.79−2.84 (m, 1H, H-10), 3.13 (q, *J* = 6.5, 1H, C*H*Me), 3.94 (br d, *J* = 13.2 Hz, 1H, H-5), 4.05 (br d, *J* = 13.2 Hz, 1H, H-5), 4.55 (br d, *J* = 4.3 Hz, 1H, H-1), 4.64 (br d, *J* = 6.2 Hz, 1H, H-4), 6.11−6.14 (m, 1H, H-9), 6.21−6.23 (m, 1H, H-8), 6.64−6.69 (m, 1H, H-7), 7.40−7.45 (m, 5H, Ph), {*minor conformer*} 1.49 (d, *J* = 6.5 Hz, 3H, Me), 2.19 (br d, *J* = 11.1 Hz, 1H, H-10), 2.55−2.62 (m, 1H, H-10), 3.77 (q, *J* = 6.5 Hz, 1H, C*H*Me), 3.94 (br d, *J* = 13.2 Hz, 1H, H-5), 4.13 (br d, *J* = 13.2 Hz, 1H, H-5), 4.16 (br s, 1H, H-1), 4.95 (br s, 1H, H-4), 5.65−5.70 (m, 1H, H-9), 6.05−6.09 (m, 1H, H-8), 6.47−6.52 (m, 1H, H-7), 7.18−7.41 (m, 5H, Ph); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) {*major conformer*} 21.4 (q), 36.1 (t),

53.0 (t), 54.5 (d), 63.0 (d), 72.0 (t), 106.3 (d), 107.8 (d), 119.7 (d), 126.7 (d), 127.0 (d), 127.4 (s), 128.0 (d), 144.3 (s), {*minor conformer*} 21.2 (q), 31.8 (t), 52.1 (t), 55.0 (d), 66.5 (d), 73.8 (d), 102.7 (d), 108.0 (d), 119.1 (d), 126.7 (d), 127.3 (d), 127.4 (s), 128.5 (d), 143.3 (s); MS *m*/*z* 254 (M^+). Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.55; H, 7.14; N, 11.02. Found: C, 75.63; H, 7.03; N, 11.13. The last fraction contained 0.23 g (24%) of (+)-(α*R*,1*R*,4*S*)-2-(α-phenylethyl)-1,2,4,5-tetrahydro-1,4-methanopyrrolo[2,1-*d*][1,2,5]oxadiazepine (**19**) isolated as an oil: $[\alpha]_D$ = +25.4 (*c* = 0.10, $CHCl_3$);^{1}H NMR (δ, $CDCl_3$, 300 MHz, *T* = −40 °C) 1.42 (d, *J* = 6.4 Hz, 3H, Me), 2.14 (br d, *J* = 10.9 Hz, 1H, H-10), 2.79 (ddd, *J* = 4.8, 6.5, 10.9 Hz, 1H, H-10), 3.28 (q, *J* = 6.4 Hz, 1H, C*H*Me), 3.98 (br d, *J* = 12.0 Hz, 1H, H-5), 4.12 (br d, *J* = 12.0 Hz, 1H, H-5), 4.11 (br d, *J* = 4.8 Hz, 1H, H-1), 4.82 (ddd, *J* = 2.1, 2.2, 6.5 Hz, 1H, H-4), 5.61 (dd, *J* = 1.4, 3.5 Hz, 1H, H-9), 6.14 (dd, *J* = 2.7, 3.5 Hz, 1H, H-8), 6.64 (dd, *J* = 1.4, 2.7 Hz, 1H, H-7), 7.21−7.34 (m, 5H, Ph); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 23.1 (q), 36.3 (t), 53.2 (t), 54.6 (d), 63.4 (d), 72.5 (d), 107.3 (d), 107.7 (d), 119.4 (d), 127.1 (d), 127.4 (s), 127.7 (d), 128.1 (d), 143.1 (s); MS *m*/*z* 254 (M^+). Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.55; H, 7.14; N, 11.02. Found: C, 75.49; H, 7.05; N, 10.91.

(+)-(6*R*)-6-Hydroxy-5,6,7,8-tetrahydroindolizidine (10). Obtained in 68% yield from **18** according to the procedure described for the racemate. $[\alpha]_D$ = +36.1 (*c* = 0.14, $CHCl_3$). Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.92; H, 7.98; N, 10.11.

(−)-(6*S*)-6-Hydroxy-5,6,7,8-tetrahydroindolizidine (10). Obtained in 65% yield from **19** according to the procedure described for the racemate. $[\alpha]_D$ = −31.1 (*c* = 0.18, $CHCl_3$). Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.16; H, 8.16; N, 10.29.

(+)-(6*R*,8a*R*)-6-Hydroxy-1,2,3,5,6,7,8,8a-octahydroindolizidine (13). Obtained in 27% yield from **18** according to the procedure described for the racemate. $[\alpha]_D$ = +23.1 (*c* = 0.17, $CHCl_3$). Anal. Calcd for: $C_8H_{15}NO$: C, 68.03; H, 10.71; N, 9.92. Found: C, 67.95; H, 10.60; N, 9.81.

(+)-(6*R*,8a*S*)-6-Hydroxy-1,2,3,5,6,7,8,8a-octahydroindolizine (14). Obtained in 21% yield from **18** according to the procedure described for the racemate. $[\alpha]_D$ = +24.7 (*c* = 0.16, $CHCl_3$). Anal. Calcd for: $C_8H_{15}NO$: C, 68.03; H, 10.71; N, 9.92. Found: C, 67.87; H, 10.83; N, 9.79. A solution of (+)-**14** (10 mg, 0.07 mmol) and (+)-(2*R*,3*R*)-dibenzoyltartaric anhydride (24 mg, 0.07 mmol) in CH_2Cl_2 (2 mL) was stirred for 48 h. The solvent was evaporated to give the crude monoester: ^{1}H NMR (δ, CD_3OD, 300 MHz) 1.50−2.30 (overlapping, 11H), 3.10−3.55 (overlapping, 2H), 5.06−5.14 (m, 1H), 5.71 (d, *J* = 5.6 Hz, 1H), 5.79 (d, *J* = 5.6 Hz, 1H), 7.42−7.67 (m, 6H), 7.98−8.12 (m, 4H); MS *m*/*z* 481 (M^+).

(−)-(6*S*,8a*S*)-6-Hydroxy-1,2,3,5,6,7,8,8a-octahydroindolizidine (13). Obtained in 28% yield from **19** according to the procedure described for the racemate. $[\alpha]_D$ = −23.4 (*c* = 0.16, $CHCl_3$). Anal. Calcd for $C_8H_{15}NO$: C, 68.03; H, 10.71; N, 9.92. Found: C, 68.11; H, 10.85; N, 10.06.

(−)-(6*R*,8a*S*)-6-Hydroxy-1,2,3,5,6,7,8,8a-octahydroindolizine (14). Obtained in 24% yield from **19** according to the procedure described for the racemate. $[\alpha]_D$ = −26.6 (*c* = 0.16, $CHCl_3$). Anal. Calcd for $C_8H_{15}NO$: C, 68.03; H, 10.71; N, 9.92. Found: C, 67.94; H, 10.58; N, 9.80. Treatment of (−)-**14** with (+)−(2*R*,3*R*)-dibenzoyltartaric anhydride, as described for its enantiomer, gave the crude monoester: ^{1}H NMR (δ, CD_3OD, 300 MHz) 1.45−2.15 (overlapping, 11H), 3.10−3.65 (overlapping, 2H), 5.15 (broad s, 1H), 6.10 (broad s, 1H), 6.22 (broad s, 1H), 7.40−7.70 (m, 6H), 7.96−8.18 (m, 4H); MS *m*/*z* 481 (M^+).

(+)-(1*S*,2*S*)-1-Amino-2,3-dihydro-1*H*-pyrrolizine-2-methanol (12). Obtained in 66% yield from **20** according to the procedure described for the racemate. $[\alpha]_D$ = +20.2 (*c* = 0.10, $CHCl_3$). Anal. Calcd for $C_8H_{12}N_2O$: C, 63.12; H, 7.95; N, 18.41. Found: C, 63.25; H, 7.79; N, 18.29.

(−)-(1*R*,2*R*)-1-Amino-2,3-dihydro-1*H*-pyrrolizine-2-methanol (12). Obtained in 59% yield from **21** according to the procedure described for the racemate. $[\alpha]_D$ = −20.7 (*c* = 0.10, $CHCl_3$). Anal. Calcd for $C_8H_{12}N_2O$: C, 63.12; H, 7.95; N, 18.41. Found: C, 62.98; H, 8.12; N, 18.32.

(+)-(2*R*,7a*S*)-2,3,5,6,7,7a-Hexahydro-1*H*-pyrrolizine-2-methanol (15). Obtained in 46% yield from **20** according to the procedure described for the racemate. $[\alpha]_D$ = +20.5 (*c* = 0.10, $CHCl_3$). Anal. Calcd for $C_8H_{15}NO$: C, 68.03; H, 10.71; N, 9.92. Found: C, 67.86; H, 10.58; N, 10.08.

(−)-(2*S*,7a*R*)-2,3,5,6,7,7a-Hexahydro-1*H*-pyrrolizine-2-methanol (15). Obtained in 52% yield from **21** according to the procedure described for the racemate. $[\alpha]_D$ = −20.8 (*c* = 0.34, $CHCl_3$). Anal. Calcd for $C_8H_{15}NO$: C, 68.03; H, 10.71; N, 9.92. Found: C, 68.15; H, 10.87; N, 9.84.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for compounds **7**−**10**, **12**−**15**, and **18**−**21** as well as of two-dimensional NMR spectra for compounds **13**−**15** (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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