Access to Pyrrolo- and Pyrido[1,2-*a*]indole Derivatives by Intramolecular Nitrone Cycloadditions. Effect of Steric Factors on the Regioselective Product Formation

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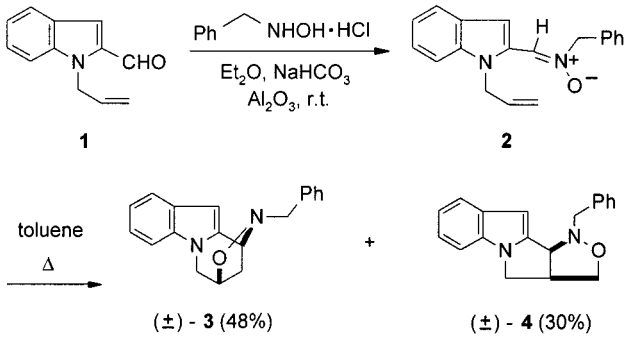
On starting from *N*-allyl-substituted 2-indolecarbaldehydes and exploiting the intramolecular nitrone cycloaddition methodology, we synthesized a number of the title fused-ring indole derivatives in racemic as well as enantiopure form.

Introduction

The indole nucleus annulated to carbocyclic or heterocyclic ring(s) is present in an astonishing variety of natural products endowed with potent and multiform biological activities.[1−6] Hence, novel and efficient syntheses of such compounds still represent highly pursued targets. In recent years, one of us has just reported synthetic studies dealing with indole and carbazole alkaloids,[7−9] while some of us have successfully tried for applications of the intramolecular nitrone cycloaddition methodology.[10,11] On these grounds, we have decided to exploit the same methodology as a tool for the conversion of simple and easily accessible indoles to more complex, polycyclic indole derivatives structurally related to natural or synthetic bioactive compounds. In particular, we have aimed at the construction of a functionalized ring annulated to the 1,2-position of the indole nucleus in the light of the fact that such a skeleton is present in mitosenes and mitomycins. These compounds show antibiotic and antitumor activity and inhibit bacterial cell division through a mechanism of DNA alkylation.[12−14] In particular, mitomycin C is used in clinical cancer chemotherapy.

Scheme 1



Nitrones derived from 1-allyl-2-indolecarbaldehyde (**1**) were perceived as suitable intermediates for our purpose (Scheme 1).

As a function of the regiochemical outcome of the intramolecular cycloaddition, both pyrrolo- and pyrido-[1,2-*a*]indole skeletons were accessible by the approach here described.

Results and Discussion

Treatment of aldehyde **1** with benzylhydroxylamine, carried out in diethyl ether at room temperature, allowed the isolation of the pure nitrone **2** in 45% yield. Heating

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the latter in refluxing toluene resulted in a mixture of the two regioisomeric cycloadducts **3** and **4**, which were isolated by column chromatography in 48 and 30% yield, respectively. Structural assignments to the products came from analytical and spectroscopic data. In particular, the ^{13}C NMR spectrum of **4** shows triplet signals at 48.7, 60.3 and 72.6 ppm, thus indicating that all methylene groups are adjacent to heteroatom. It is not so in the case of **3** because its ^{13}C NMR spectrum has a triplet signal at ca.. 30 ppm, which corresponds to a methylene group adjacent to carbons.[15,16] The cis junction of the two new rings in both cycloadducts **3** and **4** is clearly the consequence of geometric restraints imposed by the intramolecular approach.

The preferred formation of the strained bridged-ring species **3** is worthy of noting, particularly in light of the behavior of *C*-(1-allyl-3-methylindol-2-yl)-*N*-methylnitrone, which has been reported to give only a fused-ring intramolecular cycloadduct.[17,18] A possible explanation followed from the inspection of molecular models. The conformation of the reactant with the allyl moiety folded toward the inside is rather crowded and plausibly disfavored with respect to the conformation having the allyl moiety oriented externally. However, the latter conformation (which would originate **4**) seems less suitable to the intramolecular approach of the π systems in parallel planes and consequently may well be less reactive than the former conformation (just leading to **3**). To support this view, we decided to perform a MM+ treatment. Such a technique, often inadeguate to construct transition states, was believed to be reliable in our case because geometric constraints and steric factors more than electronic features should be determinant to differentiate the regioisomeric pathways. In light of theoretical studies of 1,3-dipolar cycloadditions,[19−21] three different hypotheses were taken into account: (i) a synchronous approach with a distance of 2.85 Å for each pair of reaction centers, (ii) an asynchronous approach with the C−O distance shorter than the C−C one (2.7 vs 3.0 Å), and (iii) an asynchronous approach with the C−O distance longer than the C−C one (3.0 vs 2.7 Å). For both the bridged-ring and the fused-ring approaches, the situation (ii) was found to be the most favorable. However, the fused-ring conformation **B** was higher in energy by 0.4 kcal/mol with respect to the bridged-ring conformation **A** (Figure 1). Such a difference in activation energies should determine a product ratio **3**:**4** of ca. 1.7:1.

Aiming to gain deeper information about the regiochemical aspect of the intramolecular cycloaddition, we

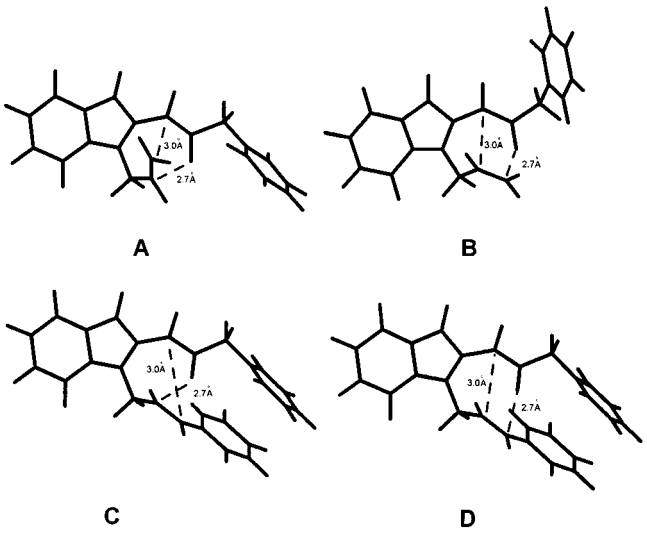
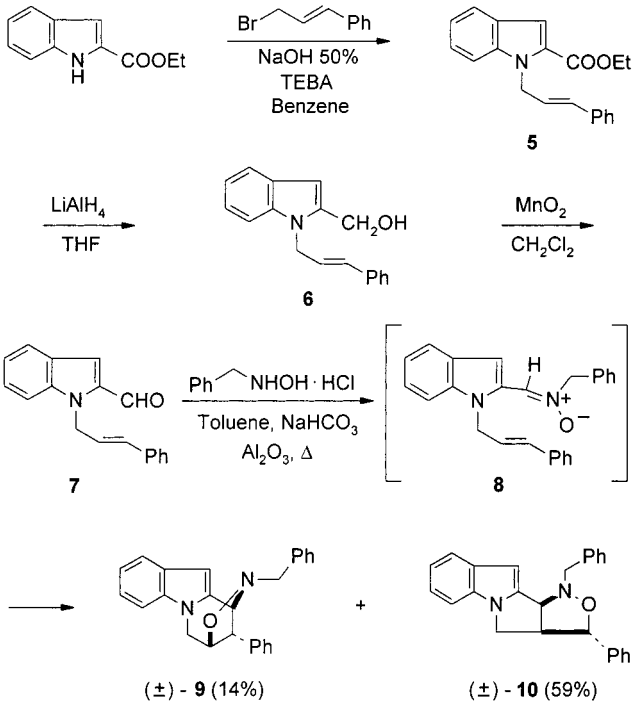


Figure 1. "Bridged-ring" and "fused-ring" regioisomeric approaches for the intramolecular cycloadditions of nitrones **2** and **8**.

Scheme 2



synthesized the cinnamyl-substituted aldehyde **7** and treated it with benzylhydroxylamine (Scheme 2). The reaction was rather difficult and required heating, so that the corresponding nitrone **8** behave as a transient species. Actually, after toluene refluxing for 5 days, the isolated products were **9** (14%) and **10** (59%). Once again, by means of MM+ computations, the asynchronous path with the C−O distance shorter than the C−C one was estimated as the most favored for both regioisomeric possibilities. However, the fused-ring conformation **D** was lower in energy by 0.7 kcal/mol with respect to the bridged-ring conformation **C** (Figure 1). One can therefore deduce that the regioselective preference of nitrones **2** and **8** is markedly dependent on steric interactions. On the other hand, the interplay between the intrinsic stereoretention of concerted cycloadditions and the geometric constraints due to the intramolecularity dictates

(15) Compound **3** exists as a 5:1 mixture of two conformers which present differentiate NMR signals. They are plausibly due to hindered inversion at the pyramidal nitrogen in accord with literature precedents concerning encumbered isoxazolidines (see ref 16). A conformational study by the MM+ method has indicated that the invertomer with the *N*-pendant in pseudoaxial position is more stable of 2.6 kcal/mol in comparison to the one having the *N*-pendant in pseudoequatorial position.

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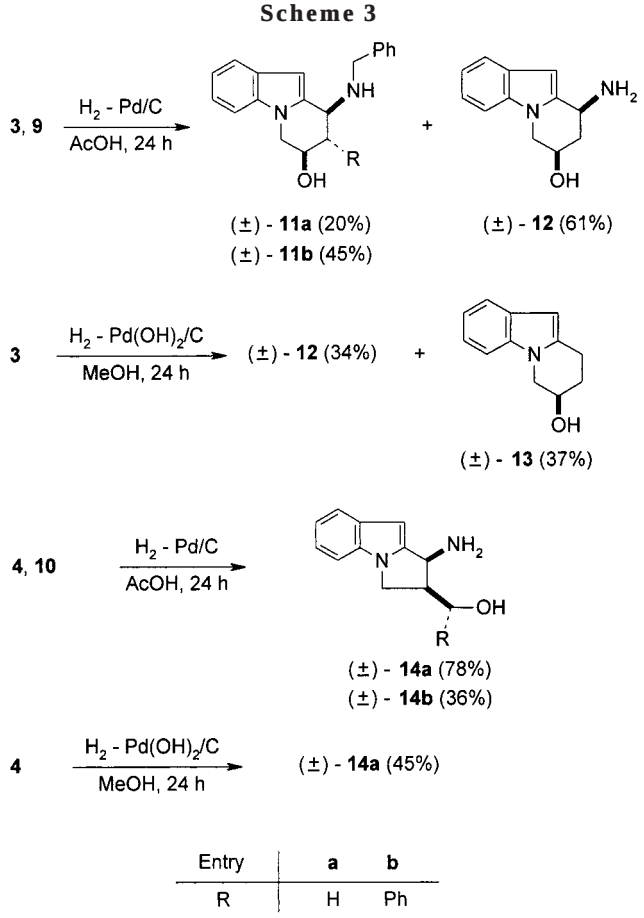
Scheme 3



the relative configuration of the three new stereocenters of **9** and **10**. Such a total stereoselection just constitutes a remarkable advantage from the synthetic point of view.[22]

The above cycloadducts were submitted to reductive cleavage of the isoxazolidine ring in order to bring to light its latent functionalities. Among the possible procedures,[23] we chose the catalytic hydrogenation having in mind the concomitant debenzylation. The array of our experimental findings is outlined in Scheme 3. In the case of the bridged-ring substrates **3** and **9**, the removal of a benzylic group was incomplete when operating with Pd/C in AcOH. On the other hand, when using $Pd(OH)_2$ in MeOH, the disappointing loss of the pseudobenzylic amino group was observed.

The subsequent stage of our work was aimed at the preparation of nonracemic compounds by means of the enantiopure benzyl-like hydroxylamine **15** as the reaction partner toward aldehydes **1** and **7** (Scheme 4). In both cases, the intramolecular cycloaddition of the first-formed nitrone **16** gave four isomeric products: two having a bridged-ring structure and two having a fused-ring structure. The proportions between the two kinds of products practically matched those observed in the intramolecular cycloadditions of the related *N*-benzylnitrones **2** and **8**. Within each pair of diastereoisomers, the

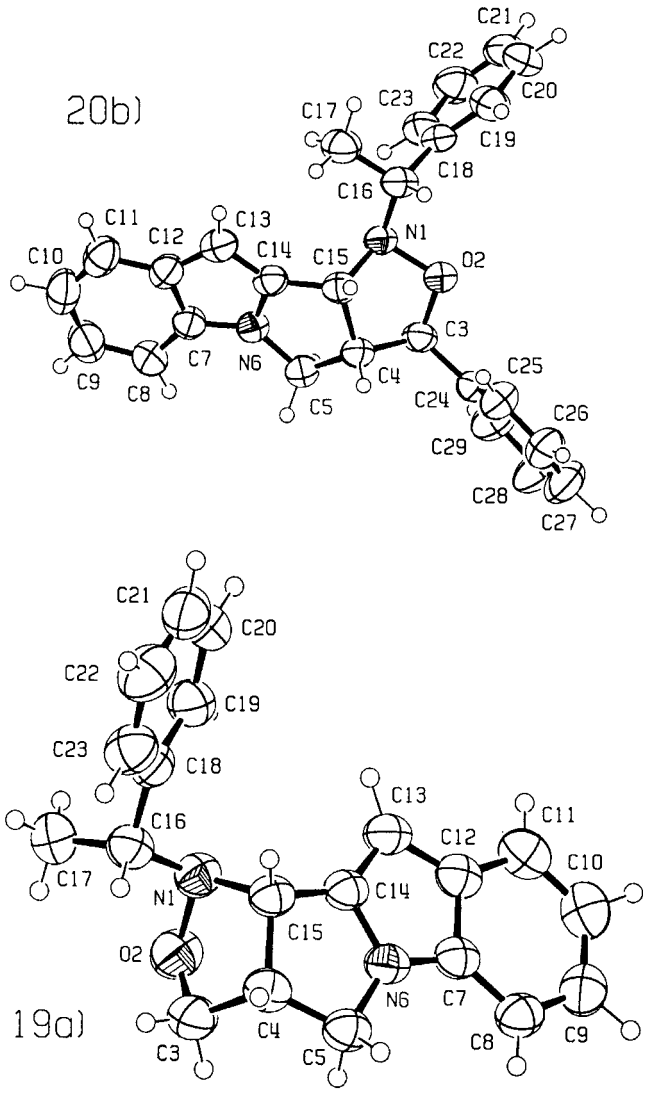


Figure 2. X-ray diffractometric analysis of fused-ring cycloadducts **19a** and **20b**.

ratio deduced by the NMR spectrum of the product mixture was approximatively 3:2, due to some degree of asymmetric induction exerted by the chiral auxiliary. It must be emphasized that the major bridged-ring product arising from **16a** exists as a mixture of two conformers with different NMR signals, which give coalescence at 35 °C.

The distinction between the two diastereoisomeric fused-ring structures was easily made by submitting **19a** and **20b** to X-ray diffractometric analysis (Figure 2).[24] In the case of the bridged-ring structures, where suitable crystalline samples were not available, absolute configurations were inferred from a conformational study associated with the comparative examination of the NMR properties. We applied the MM^+ procedure to the conformational analysis of the diastereoisomeric structures **17a** and **18a**. In both cases, two energy minima were found in correspondence to the pseudoaxial and pseudoequatorial disposition of the *N*-pendant; however, the

(22) It remains to be noticed that compound **9** does not exhibit splitting of the NMR signals, even at −60 °C, thus indicating the existence of only one conformer. On the basis of MM^+ computations, the invertomer with the *N*-pendant in pseudoaxial position was shown to be energetically favoured, as already found for the analogous compound **3**.

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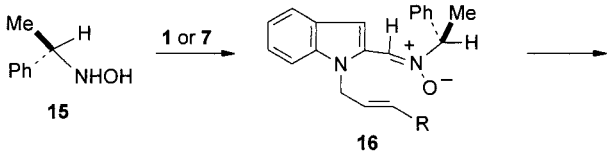
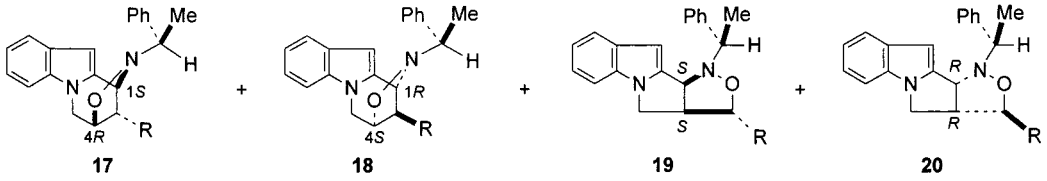
Scheme 4





Entry	R	Products and yields (%)			
		17	**18**	**19**	**20**
a	H	27	21	17	9
b	Ph	8	2	29	13

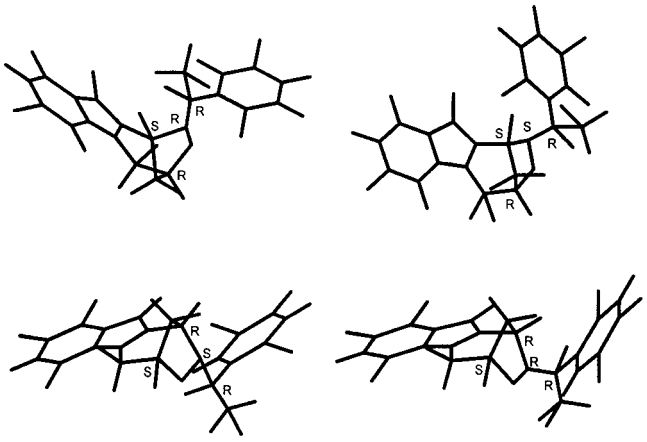


Figure 3. Energy minimum conformations of the bridged-ring cycloadducts **17** and **18** as inferred from MM$^+$ computations.

Table 1. Chemical Shifts of the Pyrrolic Hydrogen in Bridged- and Fused-Ring Cycloadducts 17−20

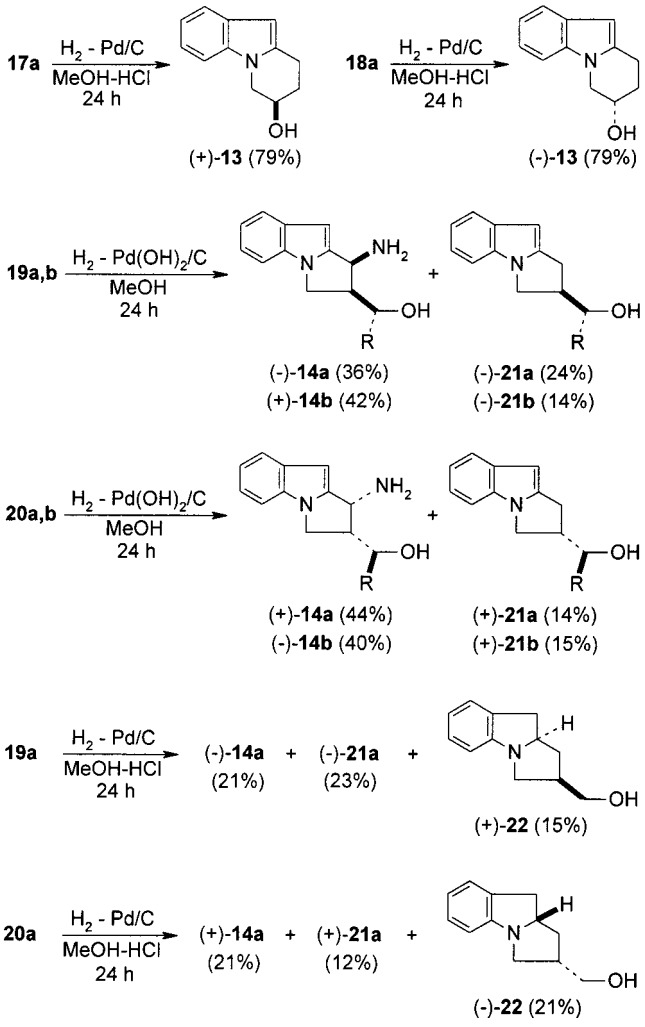
entry	17	18	19	20
a	6.53[a] 6.09[b]	5.98	5.93	6.31
b	6.42	5.94	5.08	6.18

[a] Major conformer. [b] Minor conformer.

first conformation was determined to be more stable by 0.7 kcal/mol in **17a** and by 2.8 kcal/mol in **18a** (Figure 3). The 1*S*,4*R* absolute configuration (**17a**) was then assigned to the diastereoisomer existing as a mixture of two conformers. Such an assignment was corroborated by the chemical shifts of the pyrrolic hydrogen, whose upfield resonance reflects its positioning in the shielding region of a phenyl ring, as demonstrated by the X-ray analysis of **19a**. The observed values (Table 1) are in perfect agreement with the conformational formulas depicted in Figure 3. In light of the full analogy of the NMR data, we were able to confidently assign absolute configurations in the case of **17b** and **18b**.

As the final stage of our work, we submitted the optically active cycloadducts **17a**, **18a**, **19a**,**b**, and **20a**,**b** to catalytic hydrogenation. Once again, the choice of the experimental conditions was subtle in order to realize a selective reaction. The observed outcomes are summarized in Scheme 5. The presence of a strong protic acid was advisable, in the case of the bridged-ring cycload-

Scheme 5



ducts, to avoid long reaction times (several days). On the other side, however, it facilitated the loss of the pseudobenzylic amino group as well as the hydrogenation of the pyrrole nucleus. It is noteworthy that the formation of **22**, which implies the creation of a new stereocenter, was fully stereoselective, probably due to steric factors favoring the anti disposition of the bridgehead hydrogen with respect to the hydroxymethyl group. Such a configuration has been elucidated by NOESY measurements.

The enantiomeric purity was verified in the case of amino alcohol (+)-**14b** on recording the ^{1}H NMR spectrum in the presence of (*R*)-*O*-acetylmandelic acid and in the case of alcohols (−)-**21a** and (−)-**21b** by treatment with Mosher's (*R*)-acid chloride and subsequent ^{1}H NMR analysis.

Conclusions

Although the results presented here show some degree of variability, particularly as the final hydrogenation step is concerned, there is no doubt that they are satisfactory in view of the planned target. Actually, we succeeded in synthesizing a number of enantiopure representatives of the title fused-ring indole systems by way of a short and efficient reaction sequence.

Experimental Section

Melting points were measured in open capillary tubes and are uncorrected. IR spectra were recorded using FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR chemical shifts are given in ppm downfield from $SiMe_4$. Mass spectra were taken at 70 eV by E. I. method. The optical rotations were determined on a digital polarimeter, with a 1 dm path length at 25 °C; concentrations (*c*) were reported in g/100 mL.

1-Allyl-2-hydroxymethylindole. A solution of 1-allyl-2-carbethoxyindole[25] (5.10 g, 21.1 mmol) in dry THF (40 mL) was dropped, under N_2, in an ice-cooled suspension of $LiAlH_4$ (1.01 g, 26.6 mmol) in dry THF (40 mL). The mixture was heated at reflux for 1 h. MeOH (10 mL) was slowly added and the solvent was removed under reduced pressure. After addition of water (20 mL), the aqueous layer was adjusted to pH 7 with 0.1 M HCl and extracted with CH_2Cl_2. The organic solution was dried over Na_2SO_4 and evaporated to give 3.23 g (79%) of the title compound: oil; ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 2.16 (br s, 1H, missing after deuteriation), 4.79 (s, 2H), 4.84−4.90 (overlapping, 3H), 5.12 (dd, J = 1.2, 10.1 Hz, 1H), 5.99 (tdd, J = 4.9, 10.1, 17.4 Hz, 1H), 6.48 (s, 1H), 7.15 (dd, J = 7.4, 7.7 Hz, 1H), 7.20−7.41 (overlapping, 2H), 7.59 (d, J = 7.7 Hz, 1H); IR (Nujol) 3325 cm^{-1}; MS *m*/*z* 187 (M^+). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 77.09; H, 6.87; N, 7.07.

1-Allylindole-2-carbaldehyde (1). Activated MnO_2 (28.4 g, 32.6 mmol) was added to a solution of 1-allyl-2-hydroxymethylindole (3.23 g, 17.2 mmol) in CH_2Cl_2 (120 mL). The mixture was stirred at room temperature for 3 h and filtered over a short path of Celite, which was subsequently washed with CH_2Cl_2 several times. The filtrate was evaporated to give 2.79 g (88%) of (**1**).[26]

***N*-[(1-Allylindol-2-yl)methylene]benzenemethanamine *N*-Oxide (2).** A suspension of *N*-benzylhydroxylamine hydrochloride (660 mg, 4.1 mmol), Al_2O_3 (8.0 g), and $NaHCO_3$ (570 mg, 6.8 mmol) in Et_2O (40 mL) was stirred at room temperature for 1 h. A solution of **1** (590 mg, 3.2 mmol) in Et_2O (20 mL) was added, and the resulting mixture was stirred for 48 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 410 mg (45%) of **2**: mp 94−96 °C (diisopropyl ether); ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 4.42 (overlapping, 2H), 4.72 (dd, J = 1.2, 17.1 Hz, 1H), 5.06 (dd, J = 1.2, 10.4 Hz, 1H), 5.10 (s, 2H), 5.82 (tdd, J = 4.7, 10.4, 17.1 Hz, 1H), 7.10 (ddd, J = 1.6, 6.3, 8.0 Hz, 1H), 7.20−7.46 (overlapping, 8H), 7.68 (d, J = 8.0 Hz, 1H), 8.21 (s, 1H); MS *m*/*z* 290 (M^+). Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.65; H, 6.28; N, 9.50.

Intramolecular Cycloaddition of Nitrone 2. A solution of **2** (540 mg, 1.8 mmol) in toluene (55 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 160 mg (30%) of (3a*R**,10b*R**)-1-benzyl-1,3a,4,10b-tetrahydro-3*H*-isoxazolo[3′,4′:3,4]pyrrolo[1,2-*a*]indole (**4**): mp 131−132 °C (hexane−benzene); ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 3.91 (dd, J = 4.2, 8.7 Hz, 1H), 3.99−4.07 (m, 1H), 4.11 (dd, J = 3.6, 10.2 Hz, 1H), 4.12 and 4.19 (AB system, J = 13.2 Hz, 2H), 4.27 (dd, J = 8.1, 10.2 Hz, 1H), 4.35 (br s, 1H), 4.70 (br s, 1H), 6.13 (s, 1H), 7.06 (dd, J = 7.1, 7.1 Hz, 1H), 7.14 (dd, J = 7.0, 7.0 Hz, 1H), 7.28−7.46 (overlapping, 6H), 7.55 (d, J = 7.8 Hz, 1H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 48.68 (t), 50.85 (d), 60.34 (t), 67.29 (d), 72.56 (t), 94.97 (d), 109.68 (d), 119.62 (d), 121.18 (d), 127.55 (d), 128.46 (d), 129.11 (d), 132.58 (s), 133.22 (s), 137.02 (s), 141.21 (s); MS *m*/*z* 290 (M^+). Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.45; H, 6.39; N, 9.76. The last fractions contained 260 mg (48%) of (1*R**,4*S**)-2-benzyl-1,2,4,5-tetrahydro-1,4-methanoindolo[2,1-*d*][1,2,5]oxadiazepine (**3**): mp 131−132 °C (hexane−benzene); ^{1}H NMR (δ, $CDCl_3$, 300 MHz) major conformer 2.32 (d, J = 10.9 Hz, 1H), 2.85−3.00 (m, 1H), 3.57 and 3.67 (AB system, J = 12.4 Hz, 2H), 4.03 (d, J = 11.8 Hz, 1H), 4.27 (d, J = 11.8 Hz, 1H), 4.50 (d, J = 4.5 Hz, 1H), 4.93 (br d, J = 6.5 Hz, 1H), 6.33 (br s, 1H), 7.10−7.37 (overlapping, 8H), 7.60−7.67 (m, 1H); minor conformer 2.32 (d, J = 10.9 Hz, 1H), 2.75−2.85 (m, 1H), 3.57 and 3.67 (AB system, J = 12.4 Hz, 2H), 3.89−4.03 (m, 1H), 4.10−4.17 (m, 1H), 4.50 (d, J = 4.5 Hz, 1H), 5.03−5.14 (m, 1H), 6.23 (br s, 1H), 7.10−7.37 (overlapping, 8H), 7.60−7.67 (m, 1H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) major conformer 30.92 (t), 51.20 (t), 54.55 (t), 59.57 (d), 68.11 (d), 90.94 (d), 108.98 (d), 119.88 (d), 120.83 (d), 122.30 (d), 127.41 (d), 128.46 (d), 129.06 (d), 132.22 (s), 136.30 (s), 143.91 (s); minor conformer 30.43 (t), 50.63 (t), 56.32 (t), 57.81 (d), 68.45 (d), 93.11 (d), 109.37 (d), 120.22 (d), 121.33 (d), 122.30 (d), 127.41 (d), 128.46 (d), 129.06 (d), 129.96 (s), 131.76 (s), 136.01 (s), 142.64 (s); MS *m*/*z* 290 (M^+). Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.51; H, 6.18; N, 9.81.

1-Cinnamyl-2-carbethoxyindole (5). Cinnamyl bromide (3.15 g, 16 mmol), TEBA (110 mg, 0.5 mmol), and 50% NaOH (20 mL) were added to a solution of 2-carbethoxyindole (2.00 g, 10 mmol) in benzene (64 mL). The mixture was vigorously stirred at room temperature for 1 h. The organic layer was separated, washed with water, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give 1.46 g (48%) of **5**: mp 72−73 °C (diisopropyl ether); ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 1.43 (t, J = 7.1 Hz, 3H), 4.40 (q, J = 7.1 Hz, 2H), 5.41 (d, J = 4.0 Hz, 2H), 6.41 (overlapping, 2H), 7.15−7.40 (overlapping, 8H), 7.46 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H); IR (Nujol) 1710 cm^{-1}; MS *m*/*z* 305 (M^+). Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.59; H, 6.37; N, 4.40.

1-Cinnamyl-2-hydroxymethylindole (6). A solution of **5** (220 mg, 0.73 mmol) in dry THF (5 mL) was dropped, under N_2, in a suspension of $LiAlH_4$ (34 mg, 0.88 mmol) in dry THF (40 mL) at 0 °C. The mixture was stirred at room temperature for 2 h. MeOH (1 mL) was slowly added, and the solvent was removed under reduced pressure. After addition of water (2 mL), the aqueous layer was adjusted to pH 7 with 0.1 M HCl and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated to give 150 mg (78%) of **6**: mp 99−100 °C (diisopropyl ether); ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 1.57 (br s, 1H, missing after deuteriation), 4.79 (s, 2H), 4.85 (d, J = 3.4 Hz, 2H, s after deuteriation), 5.05 (d, J = 3.1 Hz, 2H), 6.35−6.38 (overlapping, 2H), 6.53 (s, 1H), 7.13 (dd, J = 7.0, 7.0 Hz, 1H), 7.21−7.32 (overlapping, 6H), 7.39 (d, J = 8.1 Hz,

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1H), 7.64 (d, J = 7.8 Hz, 1H); IR (Nujol) 3390 cm^{-1}; MS m/z 263 (M^+). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.98; H, 6.62; N, 5.37.

1-Cinnamylindole-2-carbaldehyde (7). Activated MnO_2 (940 mg, 10.8 mmol) was added to a solution of **6** (150 mg, 0.57 mmol) in CH_2Cl_2 (6 mL). The mixture was stirred at room temperature for 12 h and filtered over a short path of Celite, which was subsequently washed with CH_2Cl_2 several times. The filtrate was evaporated to give 78 mg (52%) of **7**: mp 71−72 °C (diisopropyl ether); ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 5.41 (d, J = 4.9 Hz, 2H), 6.30−6.50 (overlapping, 2H), 7.18−7.35 (overlapping, 7H), 7.43−7.51 (overlapping, 2H), 7.79 (d, J = 8.1 Hz, 1H), 9.94 (s, 1H); IR (Nujol) 1670 cm^{-1}; MS m/z 261 (M^+). Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.59; H, 5.87; N, 5.52.

Reaction of 7 with *N*-Benzylhydroxylamine. A suspension of **7** (460 mg, 1.8 mmol), *N*-benzylhydroxylamine hydrochloride (360 mg, 2.3 mmol), Al_2O_3 (4.2 g), and $NaHCO_3$ (300 mg, 3.8 mmol) in toluene (130 mL) was refluxed for 5 d. After filtration through Celite and evaporation of the solvent under reduced pressure, the residue was chromatographed on a silica gel column with toluene/AcOEt (19/1) as eluent. The first fractions gave 92 mg (14%) of (1*R**,4*S**,12*R**)-2-benzyl-12-phenyl-1,2,4,5-tetrahydro-1,4-methanoindolo[2,1-*d*][1,2,5]oxadiazepine (**9**): mp 127−128 °C (hexane−benzene); ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 3.65 and 3.74 (AB system, J = 14.3 Hz, 2H), 3.77 (s, 1H), 4.22 (dd, J = 1.4, 11.9 Hz, 1H), 4.45 (dd, J = 1.4, 11.9 Hz, 1H), 4.48 (s, 1H), 4.92 (br s, 1H), 6.35 (s, 1H), 7.15−7.45 (overlapping, 11H), 7.58−7.68 (overlapping, 3H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 51.86 (t), 54.34 (d), 58.59 (t), 62.10 (d), 100.10 (d), 109.08 (d), 120.01 (d), 120.82 (d), 121.96 (d), 127.06 (d), 127.33 (d), 127.94 (s), 128.24 (d), 128.25 (d), 128.29 (d), 128.40 (d), 128.44 (d), 136.29 (s), 136.43 (s), 137.63 (s), 139.32 (s); MS m/z 366 (M^+). Anal. Calcd for $C_{25}H_{22}N_2O$: C, 81.94; H, 6.05; N, 7.64. Found: C, 81.91; H, 5.96; N, 7.45. The last fractions contained 389 mg (59%) of (3*R**,3a*R**,10b*R**)-1-benzyl-3-phenyl-1,3a,4,10b-tetrahydro-3*H*-isoxazolo[3′,4′:3,4]-pyrrolo[1,2-*a*]indole (**10**): mp 123−124 °C (hexane−benzene); ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 3.92 (dddd, J = 4.1, 7.1, 7.9, 8.0 Hz 1H), 4.20 (dd, J = 8.0, 10.3 Hz, 1H), 4.26 and 4.39 (AB system, J = 13.1 Hz, 2H), 4.27 (dd, J = 4.1, 10.3 Hz, 1H), 4.68 (d, J = 7.9 Hz, 1H), 4.99 (d, J = 7.1 Hz, 1H), 5.78 (br s, 1H), 7.07 (ddd, J = 1.3, 8.0, 8.0 Hz, 1H), 7.15 (ddd, J = 1.1, 7.2, 8.1 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.30−7.49 (overlapping, 10H), 7.51 (d, J = 7.8 Hz, 1H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 47.34 (t), 59.95 (d), 62.32 (t), 69.44 (d), 86.31 (d), 95.63 (d), 110.36 (d), 120.33 (d), 121.90 (d), 127.41 (d), 128.36 (d), 129.09 (d), 129.12 (d), 129.16 (d), 129.39 (d), 130.40 (d), 133.27 (s), 133.71 (s), 137.14 (s), 139.14 (s), 141.50 (s); MS m/z 366 (M^+). Anal. Calcd for $C_{25}H_{22}N_2O$: C, 81.94; H, 6.05; N, 7.64. Found: C, 82.00; H, 6.21; N, 7.48.

Hydrogenation of 3 in AcOH. A mixture of 10% Pd/C (220 mg) and **3** (270 mg, 0.9 mmol) in AcOH (35 mL) was stirred under H_2 for 24 h. After filtration through Celite, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column. Elution with chloroform/methanol (1/1) gave 53 mg (20%) of (7*R**,9*S**)-9-benzylamino-7-hydroxy-6,7,8,9-tetrahydropyrido[1,2-*a*]indole (**11a**): mp 143−145 °C (diisopropyl ether); ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 1.55 (br s, 2H, missing after deuteriation), 1.90 (ddd, J = 3.0, 3.0, 14.4 Hz, 1H), 2.56 (ddd, J = 2.4, 2.4, 14.4 Hz, 1H), 3.91 and 4.03 (AB system, J = 13.0 Hz, 2H), 3.97 (dd, J = 12.0, 15.5 Hz, 1H), 4.41−4.44 (m, 1H), 4.51 (overlapping, 2H), 6.40 (s, 1H), 7.12 (dd, J = 7.4, 7.8 Hz, 1H), 7.21 (dd, J = 7.4, 7.8 Hz, 1H), 7.25−7.37 (overlapping, 6H), 7.58 (d, J = 7.8 Hz, 1H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 29.15 (t), 50.27 (d), 50.42 (t), 51.37 (t), 65.07 (d), 100.07 (d), 109.41 (d), 120.10 (d), 120.41 (d), 121.65 (d), 127.47 (d), 128.15 (d), 128.69 (d), 128.80 (s), 136.01 (s), 136.87 (s), 138.59 (s); IR (Nujol) 3250, 3290 cm^{-1}; MS m/z 292 (M^+). Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 77.89; H, 6.76; N, 9.71. Subsequent elution gave 110 mg (61%) of (7*R**,9*S**)-9-amino-7-hydroxy-6,7,8,9-tetrahydropyrido[1,2-*a*]indole (**12**): mp 144−146 °C (benzene−hexane); ^{1}H NMR (δ, CD_3OD, 300 MHz) 2.31 (ddd, J = 3.2, 3.2, 14.1 Hz, 1H), 2.39 (ddd, J = 2.9, 3.3, 14.1 Hz, 1H), 4.11 (dd, J = 3.5, 12.3 Hz, 1H), 4.26 (dd, J = 1.5, 12.3 Hz, 1H), 4.54−4.61 (m, 1H), 4.84 (dd, J = 3.2, 3.2 Hz, 1H), 6.66 (s, 1H), 7.09 (dd, J = 7.8, 8.0 Hz, 1H), 7.21 (dd, J = 7.8, 7.8 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H); ^{13}C NMR (δ, CD_3OD, 75 MHz) 31.22 (t), 43.79 (d), 48.39 (t), 63.23 (d), 100.94 (d), 109.00 (d), 119.99 (d), 120.40 (d), 122.22 (d), 127.85 (s), 130.22 (s), 136.84 (s); IR (Nujol) 3160, 3200, 3300 cm^{-1}; MS m/z 202 (M^+). Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.31; H, 7.15; N, 13.77.

Hydrogenation of 4 in AcOH. A mixture of 10% Pd/C (170 mg) and **4** (220 mg, 0.8 mmol) in AcOH (25 mL) was stirred under H_2 for 24 h. After filtration through Celite, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with chloroform/methanol (9/1) as eluent to give 120 mg (78%) of (2*R**,3*R**)-1-amino-2,3-dihydro-2-hydroxymethyl-1*H*-pyrrolo[1,2-*a*]indole (**14a**): mp 88−91 °C (diisopropyl ether); ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 2.51 (br s, 3H, missing after deuteriation), 3.17 (ddddd, J = 4.0, 6.6, 7.2, 7.4, 8.2 Hz, 1H), 3.90 (dd, J = 7.2, 11.7 Hz, 1H), 3.98 (dd, J = 4.0, 11.7 Hz, 1H), 4.02 (dd, J = 6.6, 10.2 Hz, 1H), 4.13 (dd, J = 8.2, 10.2 Hz, 1H), 4.75 (d, J = 7.4 Hz, 1H), 6.28 (s, 1H), 7.08 (ddd, J = 1.0, 6.9, 7.8 Hz, 1H), 7.16 (ddd, J = 1.0, 6.9, 7.9 Hz, 1H) 7.25 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 44.94 (t), 47.68 (d), 51.53 (d), 62.51 (t), 92.83 (d), 110.14 (d), 119.99 (d), 121.42 (d), 121.58 (d), 132.92 (s), 133.04 (s), 147.50 (s); IR (Nujol) 3040, 3275, 3345 cm^{-1}; MS m/z 202 (M^+). Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.15; H, 6.79; N, 13.67.

Hydrogenation of 3 in MeOH. A mixture of 10% Pd-$(OH)_2$/C (95 mg) and **3** (100 mg, 0.34 mmol) in MeOH (10 mL) was stirred under H_2 for 24 h. After filtration through Celite, the solvent was removed 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 24 mg (37%) of **13**: mp 94−96 °C (diisopropyl ether); ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 1.86 (br s, 1H, missing after deuteriation), 1.91−2.17 (overlapping, 2H), 2.97 (ddd, J = 6.4, 7.0, 16.7 Hz, 1H), 3.18 (ddd, J = 6.4, 7.4, 16.7 Hz, 1H), 3.90 (dd, J = 6.1, 11.8 Hz, 1H), 4.24 (dd, J = 4.6, 11.8 Hz, 1H), 4.36−4.44 (m, 1H), 6.23 (s, 1H), 7.08 (ddd, J = 1.0, 7.0, 7.2 Hz, 1H), 7.14 (ddd, J = 1.0, 7.0, 7.8 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 7.2 Hz, 1H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 20.49 (t), 30.10 (t), 49.39 (t), 65.95 (d), 98.23 (d), 108.94 (d), 120.14 (d), 120.26 (d), 120.83 (d), 124.52 (s), 136.07 (s), 137.51 (s); IR (Nujol) 3380 cm^{-1}; MS m/z 187 (M^+). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 77.11; H, 6.86; N, 7.62. Switching to methanol as eluant provided a second fraction of 24 mg of **12** (34%).

Hydrogenation of 4 in MeOH. A mixture of 10% Pd-$(OH)_2$/C (95 mg) and **4** (100 mg, 0.35 mmol) in MeOH (10 mL) was stirred under H_2 for 24 h. After filtration through Celite, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with chloroform/methanol (9/1) as eluent to give 32 mg (45%) of (**14a**).

Hydrogenation of 9 in AcOH. A mixture of 10% Pd/C (20 mg) and **9** (70 mg, 0.19 mmol) in AcOH (6 mL) was stirred under H_2 for 24 h. After filtration through Celite, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column. Elution with toluene/AcOEt (4/1) gave 32 mg (45%) of (7*R**,8*S**,9*R**)-9-benzylamino-7-hydroxy-8-phenyl-6,7,8,9-tetrahydropyrido[1,2-*a*]indole (**11b**): mp 121−122 °C (diisopropyl ether); ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 3.37−3.49 (m, 1H), 3.56 and 3.81 (AB system, J = 13.5 Hz, 2H), 4.08 (dd, J = 3.2, 12.1 Hz, 1H), 4.62−4.70 (overlapping, 2H), 4.91 (br s, 1H), 6.51 (s, 1H), 7.06 (overlapping, 2H), 7.12−7.50 (overlapping, 9H), 7.68 (d, J = 7.8 Hz, 1H), 7.72−7.78 (overlapping, 2H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 44.74 (d), 51.03 (t), 52.10 (t), 55.25 (d), 67.39 (d), 102.08 (d), 109.61 (d), 120.19 (d), 120.48 (d), 121.80 (d), 127.17 (d), 127.42 (d), 127.82 (d), 128.37 (d), 128.50 (d), 129.04 (d), 135.26 (s), 137.07 (s), 138.66 (s), 139.01 (s); IR (Nujol) 3250, 3290 cm^{-1}; MS m/z 368 (M^+). Anal. Calcd for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.57; N, 7.60. Found: C, 81.39; H, 6.71; N, 7.72.

Hydrogenation of 10 in AcOH. A mixture of 10% Pd/C (25 mg) and **10** (85 mg, 0.23 mmol) in AcOH (10 mL) was stirred under H_2 for 24 h. After filtration through Celite, the solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column with chloroform/methanol (4/1) as eluent to give 23 mg (36%) of (α*R**,2*R**,3*R**)-1-amino-2-(α-hydroxybenzyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (**14b**): oil; ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 2.96 (br s, 3H, missing after deuteriation), 3.31 (dddd, *J* = 7.5, 7.7, 7.8, 8.7 Hz, 1H), 3.75−3.95 (overlapping, 2H), 4.70 (d, *J* = 7.8 Hz, 1H), 4.93 (d, *J* = 8.7 Hz, 1H), 6.30 (s, 1H), 7.04−7.21 (overlapping, 3H), 7.29−7.48 (overlapping, 5H), 7.57 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 44.95 (t), 50.27 (d), 52.92 (d), 73.65 (d), 92.75 (d), 109.72 (d), 111.58 (d), 121.02 (d), 121.20 (d), 126.55 (d), 127.99 (d), 128.73 (d), 140.33 (s), 142.73 (s), 146.77 (s); MS *m*/*z* 278 (M^+). Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.58; H, 6.69; N, 9.98.

(*R*)-*N*-[(1-Allylindol-2-yl)methylene]-α-methylbenzenemethanamine *N*-oxide (16a). A suspension of (*R*)-*N*-α-methylbenzylhydroxylamine (**15**)[27] (480 mg, 2.7 mmol), aldehyde **1** (500 mg, 2.7 mmol) and Al_2O_3 (3.8 g) in Et_2O (18 mL) was stirred at room temperature for 48 h. After filtration and evaporation of the solvent under reduced pressure, the residue was chromatographed on a silica gel column with AcOEt/light petroleum (3/5) as eluent to give **16a** (310 mg, 38%): mp 124−125 °C (diisopropyl ether); $[\alpha]_D = -68.2$ (*c* = 0.16, $CHCl_3$); ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 1.92 (d, *J* = 6.9 Hz, 3H), 4.63−4.69 (overlapping, 2H), 4.78 (dd, *J* = 1.2, 17.1 Hz, 1H), 5.08 (dd, *J* = 1.2, 10.4 Hz, 1H), 5.20 (q, *J* = 6.9 Hz, 1H), 5.85 (tdd, *J* = 4.7, 10.4, 17.1 Hz, 1H), 7.09 (ddd, *J* = 1.7, 6.2, 7.9 Hz, 1H), 7.20−7.46 (overlapping, 8H), 7.66 (d, *J* = 7.9 Hz, 1H), 8.21 (s, 1H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 19.62 (q), 45.87 (t), 75.10 (d), 108.99 (d), 109.30 (d), 117.20 (s), 120.68 (d), 122.79 (d), 123.85 (d), 124.56 (d), 127.82 (d), 128.28 (d), 129.18 (d), 129.85 (s), 133.26 (d), 138.10 (s), 138.94 (s); MS *m*/*z* 304 (M^+). Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 79.11; H, 6.79; N, 9.03.

Intramolecular Cycloaddition of Nitrone 16a. A solution of **16a** (766 mg, 2.5 mmol) in toluene (80 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 69 mg (9%) of (+)−(α*R*,3a*R*,10b*R*)-1-(α-phenylethyl)-1,-3a,4,10b-tetrahydro-3*H*-isoxazolo[3′,4′:3,4]pyrrolo[1,2-*a*]indole (**20a**): mp 121−123 °C (hexane−benzene); $[\alpha]_D = +93.7$ (*c* = 0.47, $CHCl_3$); ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 1.62 (d, *J* = 6.6 Hz, 3H), 3.80 (dd, *J* = 4.7, 8.4 Hz, 1H), 3.90 (ddddd, *J* = 3.4, 4.6, 7.6, 7.9, 8.0 Hz, 1H), 4.06 (dd, *J* = 3.3, 10.3 Hz, 1H), 4.13 (q, *J* = 6.6 Hz, 1H), 4.16 (dd, *J* = 8.0, 10.3 Hz, 1H), 4.23 (dd, *J* = 7.6, 8.4 Hz, 1H), 4.74 (d, *J* = 7.9 Hz, 1H), 6.31 (s, 1H), 7.11 (ddd, *J* = 1.3, 7.8, 8.0 Hz, 1H), 7.18 (ddd, *J* = 1.1, 7.9, 8.1 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.39 (dd, *J* = 7.1, 7.6 Hz, 2H), 7.49 (d, *J* = 7.1 Hz, 2H), 7.61 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 22.61 (q), 48.03 (t), 51.11 (d), 63.09 (d), 65.04 (d), 72.06 (t), 95.47 (d), 109.65 (d), 119.58 (d), 121.08 (d), 127.17 (d), 127.33 (d), 127.41 (d), 128.36 (d), 132.59 (s), 133.12 (s), 140.21 (s), 142.93 (s); MS *m*/*z* 304 (M^+). Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 79.05; H, 6.51; N, 9.39. The second fraction contained 130 mg (17%) of (−)-(α*R*,3a*S*,10b*S*)-1-(α-phenylethyl)-1,3a,4,10b-tetrahydro-3*H*-isoxazolo[3′,4′:3,4] pyrrolo[1,2-*a*]indole (**19a**): mp 182−184 °C (hexane−benzene); $[\alpha]_D = -71.8$ (*c* = 0.12, $CHCl_3$); ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 1.53 (d, *J* = 6.5 Hz, 3H), 3.88−4.02 (overlapping, 3H), 4.09 (dd, *J* = 2.9, 10.3 Hz, 1H), 4.21 (dd, *J* = 7.8, 10.3 Hz, 1H), 4.32 (dd, *J* = 7.8, 7.8 Hz, 1H), 4.68−4.80 (m, 1H), 5.93 (br s, 1H), 7.03 (ddd, *J* = 1.1, 7.4, 7.5 Hz, 1H), 7.10 (ddd, *J* = 1.0, 7.1, 7.4 Hz, 1H), 7.18 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 7.1 Hz, 1H), 7.40 (dd, *J* = 7.1, 7.6 Hz, 2H), 7.45−7.52 (overlapping, 3H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 22.19 (q), 48.90 (t), 49.95 (d), 64.03 (d), 66.21 (d), 71.96 (t), 94.34 (d), 109.64 (d), 119.51 (d), 120.89 (d), 121.12 (d), 127.57 (d), 127.92 (d), 128.47 (d), 128.85 (d), 132.47 (s), 133.48 (s), 143.19 (s); MS *m*/*z* 304 (M^+). Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 79.01; H, 6.69; N, 9.08. The third fraction gave 207 mg (27%) of (−)-(α*R*,1*S*,4*R*)-2-(α-phenylethyl)-1,2,4,5-tetrahydro-1,4-methanoindolo[2,1-*d*][1,2,5]oxadiazepine (**17a**): mp 161−163 °C (hexane-benzene); $[\alpha]_D = -10.0$ (*c* = 0.10, $CHCl_3$); ^{1}H NMR (δ, $CDCl_3$, −10 °C, 300 MHz)[28] major conformer 1.38 (d, *J* = 6.4 Hz, 3H), 2.35 (dd, *J* = 1.5, 11.7 Hz, 1H), 2.87−2.99 (m, 1H), 3.22 (q, *J* = 6.4 Hz, 1H), 4.02 (dd, *J* = 3.6, 11.1 Hz, 1H), 4.16−4.39 (m, 1H), 4.80 (d, *J* = 4.5 Hz, 1H), 4.88 (d, *J* = 5.9 Hz, 1H), 6.53 (s, 1H), 7.05−7.48 (overlapping, 8H), 7.70 (d, *J* = 7.5 Hz, 1H); minor conformer 1.51 (d, *J* = 6.4 Hz, 3H), 2.20 (dd, *J* = 1.5, 11.7 Hz, 1H), 2.66−2.78 (m, 1H), 3.86 (q, *J* = 6.4, 1H), 4.02 (dd, *J* = 3.6, 11.1 Hz, 1H), 4.16−4.39 (m, 1H), 4.40 (d, *J* = 4.5 Hz, 1H), 5.19 (d, *J* = 5.9 Hz, 1H), 6.09 (s, 1H), 7.05−7.48 (overlapping, 8H), 7.53 (d, *J* = 7.5 Hz, 1H);^{1}H NMR (δ, $CDCl_3$, 35 °C, 300 MHz) 1.48 (d, *J* = 6.4 Hz, 3H), 2.26 (br d, *J* = 11.7 Hz, 1H), 2.81 (br s, 1H), 3.54 (br s, 1H), 3.97 (dd, *J* = 3.6, 11.1 Hz, 1H), 4.27 (d, *J* = 11.1 Hz, 1H), 4.58 (br s, 1H), 4.99 (br s, 1H), 6.28 (br s, 1H), 7.02−7.50 (overlapping, 8H), 7.61 (d, *J* = 7.5 Hz, 1H);^{13}C NMR (δ, $CDCl_3$, 75 MHz) major conformer 21.48 (q), 36.08 (t), 50.60 (t), 54.86 (d), 63.09 (d), 71.75 (d), 99.94 (d), 109.09 (d), 119.72 (d), 120.45 (d), 121.55 (d), 126.60 (d), 127.10 (d), 128.44 (d), 134.56 (s), 135.78 (s), 143.82 (s); minor conformer 21.31 (q), 31.83 (t), 49.82 (t), 55.52 (d), 66.48 (d), 73.58 (d), 96.38 (d), 108.67 (d), 119.40 (d), 120.45 (d), 121.23 (d), 126.60 (d), 127.10 (d), 127.23 (s), 128.81 (d), 137.65 (s), 143.03 (s); MS *m*/*z* 304 (M^+). Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.80; H, 6.44; N, 9.06. The last fraction contained 161 mg (21%) of (+)−(α*R*,1*R*,4*S*)-2-(α-phenylethyl)-1,2,4,5-tetrahydro-1,4-methanoindolo[2,1-*d*][1,2,5]oxadiazepine (**18a**): mp 181−183 °C (hexane−benzene); $[\alpha]_D = +141.7$ (*c* = 0.22, $CHCl_3$); ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 1.43 (d, *J* = 6.3 Hz, 3H), 2.22 (br d, *J* = 11.2 Hz, 1H), 2.90 (br s, 1H), 3.38 (br s, 1H), 4.00 (br d, *J* = 11.8 Hz, 1H), 4.24−4.41 (overlapping, 2H), 4.99 (br d, *J* = 5.8 Hz, 1H), 5.98 (br s, 1H), 7.16 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.21−7.41 (overlapping, 7H), 7.63 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 23.08 (q), 36.29 (t), 50.82 (t), 55.26 (d), 63.66 (d), 72.23 (d), 100.85 (d), 108.81 (d), 119.72 (d), 120.68 (d), 121.64 (d), 127.33 (d), 127.59 (s), 127.87 (d), 128.30 (d), 135.05 (s), 136.21 (s), 143.09 (s); MS *m*/*z* 304 (M^+). Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.95; H, 6.49; N, 9.33.

Reaction of Aldehyde 7 with (*R*)-*N*-α-Methylbenzylhydroxylamine (15). A suspension of **15** (620 mg, 4.6 mmol), **7** (1 g, 3.8 mmol), and Al_2O_3 (6.5 g) in toluene (24 mL) was refluxed for 5 d. After filtration and evaporation of the solvent under reduced pressure, the residue was chromatographed on a silica gel column with toluene as eluent. The first fraction gave 195 mg of a mixture (A) of two products which was further elaborated as indicated below. The second fraction contained 190 mg (13%) of (+)−(α*R*,3*R*,3a*R*,10b*R*)-1-(α-phenylethyl)-3-phenyl-1,3a,4,10b-tetrahydro-3*H*-isoxazolo[3′,4′:3,4]pyrrolo[1,2-*a*]indole (**20b**): mp 54−55 °C (diisopropyl ether); $[\alpha]_D = +52.0$ (*c* = 0.10, $CHCl_3$); ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 1.63 (d, *J* = 6.8 Hz, 3H), 3.66 (dddd, *J* = 3.4, 7.2, 8.0, 8.8 Hz 1H), 4.08 (dd, *J* = 8.0, 10.3 Hz, 1H), 4.21 (dd, *J* = 3.4, 10.3 Hz, 1H), 4.25 (q, *J* = 6.8 Hz, 1H), 4.60 (d, *J* = 8.8 Hz, 1H), 4.84 (d, *J* = 7.2 Hz, 1H), 6.18 (s, 1H), 7.03 (ddd, *J* = 1.1, 7.3, 7.4 Hz, 2H), 7.10 (ddd, *J* = 1.0, 6.9, 7.3 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 7.24−7.38 (overlapping, 5H), 7.45 (d, *J* = 7.4 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 21.68 (q), 46.89 (t), 59.82 (d), 65.93 (d), 85.47 (d), 95.94 (d), 110.15 (d), 120.19 (d), 121.80 (d), 127.11 (d), 127.84 (d), 128.12 (d), 128.68 (d), 128.83 (d), 129.08 (d), 133.15 (s), 133.57 (s), 139.34 (s), 142.20 (s); MS *m*/*z* 380 (M^+). Anal. Calcd for $C_{26}H_{24}N_2O$: C, 82.07; H, 6.36; N, 7.36. Found: C, 81.95; H, 6.52; N, 7.28. The third fraction gave 422 mg (29%) of (+)-(α*R*,3*S*,3a*S*,10b*S*)-1-(α-phenylethyl)-3-phenyl-1,3a,4,10b-tetrahydro-3*H*-isoxazolo[3′,4′:3,4]pyrrolo[1,2-*a*]indole (**19b**): mp

(27) Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron* **1985**, *41*, 3455.

(28) The ^{1}H NMR spectrum taken at the usual temperature showed two sets of broadening signals, whose multiplicity was not always definied. Complete coalescence was observed at 35 °C.

71−72 °C (diisopropyl ether); $[\alpha]_D = +20.0$ ($c = 0.10$, $CHCl_3$); ^1H NMR (δ, $CDCl_3$, 300 MHz) 1.63 (d, $J = 6.5$ Hz, 3H), 3.73 (dddd, $J = 2.8$, 7.6, 8.0, 8.8 Hz 1H), 3.98 (dd, $J = 7.6$, 10.2 Hz, 1H), 4.08 (dd, $J = 2.8$, 10.2 Hz, 1H), 4.13 (q, $J = 6.5$ Hz, 1H), 4.73 (d, $J = 8.8$ Hz, 1H), 4.83 (d, $J = 8.0$ Hz, 1H), 5.08 (s, 1H), 6.96 (ddd, $J = 1.0$, 7.5, 7.6 Hz, 1H), 7.05 (ddd, $J = 1.0$, 7.1, 7.2 Hz, 1H), 7.10 (dd, $J = 7.9$, 8.0 Hz, 1H), 7.26−7.49 (overlapping, 11H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 22.03 (q), 46.82 (t), 59.92 (d), 68.23 (d), 85.44 (d), 95.89 (d), 110.13 (d), 120.10 (d), 121.69 (d), 127.37 (d), 128.72 (d), 129.25 (d), 132.78 (s), 133.65 (s), 142.89 (s); MS *m*/*z* 380 (M^+). Anal. Calcd for $C_{26}H_{24}N_2O$: C, 82.07; H, 6.36; N, 7.36. Found: C, 82.21; H, 6.48; N, 7.45.

The above mixture labeled A was newly chromatographed on a silica gel column with light petroleum/diethyl ether (10/1) as eluent. The first fraction contained 29 mg (2%) of (−)-(α*R*,1*R*,4*S*,12*R*)-2-(α-phenyethyl)-12-phenyl-1,2,4,5-tetrahydro-1,4-methanoindolo[2,1-*d*][1,2,5]oxadiazepine (**18b**): mp 58−59 °C (diisopropyl ether); $[\alpha]_D = -59.7$ ($c = 0.16$, $CHCl_3$); ^1H NMR (δ, $CDCl_3$, 300 MHz) 1.41 (d, $J = 6.3$ Hz, 3H), 3.42 (q, $J = 6.3$ Hz, 1H), 3.62 (br s, 1H), 4.20 (dd, $J = 1.8$, 11.8 Hz, 1H), 4.27 (br s, 1H), 4.45 (dd, $J = 2.2$, 11.8 Hz, 1H), 4.93 (dd, $J = 1.8$, 2.2 Hz, 1H), 5.94 (s, 1H), 7.12−7.35 (overlapping, 10H), 7.41 (dd, $J = 7.0$, 7.7 Hz, 2H), 7.60 (d, $J = 8.0$ Hz, 1H), 7.62 (d, $J = 7.0$ Hz, 1H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 23.59 (q), 51.94 (t), 54.30 (d), 60.30 (d), 63.41 (d), 100.57 (d), 108.94 (d), 119.83 (d), 121.12 (d), 122.71 (d), 127.27 (d), 127.70 (d), 128.01 (d), 136.08 (s), 136.48 (s), 139.64 (s), 143.37 (s); MS *m*/*z* 380 (M^+). Anal. Calcd for $C_{26}H_{24}N_2O$: C, 82.07; H, 6.36; N, 7.36. Found: C, 82.12; H, 6.19; N, 7.52. The second fraction contained 115 mg (8%) of (+)-(α*R*,1*S*,4*R*,12*S*)-2-(α-phenylethyl)-12-phenyl-1,2,4,5-tetrahydro-1,4-methanoindolo[2,1-*d*][1,2,5]oxadiazepine (**17b**): mp 88−89 °C (diisopropyl ether); $[\alpha]_D = +132.8$ ($c = 0.12$, $CHCl_3$); ^1H NMR (δ, $CDCl_3$, 300 MHz) 1.20 (d, $J = 6.5$ Hz, 3H), 3.33 (q, $J = 6.5$ Hz, 1H), 3.68 (br s, 1H), 4.08 (dd, $J = 1.8$, 11.8 Hz, 1H), 4.31 (dd, $J = 2.0$, 11.8 Hz, 1H), 4.59 (br s, 1H), 4.80 (br s, 1H), 6.42 (br s, 1H), 7.08−7.24 (overlapping, 8H), 7.28 (dd, $J = 7.2$, 7.5 Hz, 1H), 7.36 (dd, $J = 7.0$, 7.5 Hz, 2H), 7.55 (d, $J = 7.2$ Hz, 2H), 7.61 (d, $J = 7.7$ Hz, 1H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 22.35 (q), 51.81 (t), 54.26 (d), 60.71 (d), 63.15 (d), 76.34 (d), 99.99 (d), 109.18 (d), 120.06 (d), 120.77 (d), 121.92 (d), 126.72 (d), 126.99 (d), 127.36 (d), 127.98 (s), 128.42 (d), 133.65 (s), 136.92 (s), 139.62 (s), 144.76 (s); MS *m*/*z* 380 (M^+). Anal. Calcd for $C_{26}H_{24}N_2O$: C, 82.07; H, 6.36; N, 7.36. Found: C, 81.90; H, 6.23; N, 7.50.

Hydrogenation of 17a. A mixture of 10% Pd/C (86 mg) and **17a** (100 mg, 0.33 mmol) in a 0.04 N solution of HCl in MeOH (8 mL) was stirred under H_2 for 24 h. After filtration through Celite, the solvent was removed under reduced pressure. The residue was treated with KOH and extracted with CH_2Cl_2. After evaporation of the solvent the crude product was chromatographed on silica gel. Elution with AcOEt/light petroleum (1/1) gave 49 mg (79%) of (+)−(7*R*)-7-hydroxy-6,7,8,9-tetrahydropyrido[1,2-*a*]indole (**13**): $[\alpha]_D = +18.0$ ($c = 0.10$, $CHCl_3$).

Hydrogenation of 18a. According to the procedure described in the preceding preparation, compound **18a** (107 mg, 0.35 mmol) gave 52 mg (79%) of (−)-(7*S*)-7-hydroxy-6,7,8,9-tetrahydropyrido[1,2-*a*]indole (**13**): $[\alpha]_D = -17.3$ ($c = 0.14$, $CHCl_3$).

Hydrogenation of 19a without HCl. A mixture of 10% $Pd(OH)_2$/C (87 mg) and **19a** (100 mg, 0.32 mmol) in MeOH (10 mL) was stirred under H_2 for 24 h. After filtration through Celite, the solvent was removed under reduced pressure and the crude product was chromatographed on silica gel with AcOEt/light petroleum (1/3) as eluent. The first fraction gave 14 mg (24%) of (−)-(2*R*)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indolo-2-methanol (**21a**): oil; $[\alpha]_D = -3.7$ ($c = 0.15$, $CHCl_3$); ^1H NMR (δ, $CDCl_3$, 300 MHz) 1.65 (br s, 1H, missing after deuteriation), 2.76−2.88 (m, 1H), 3.10−3.28 (overlapping, 2H), 3.71 (dd, $J = 7.2$, 10.3 Hz, 1H), 3.80 (dd, $J = 6.0$, 10.3 Hz, 1H), 3.93 (dd, $J = 5.1$, 10.2 Hz, 1H), 4.19 (dd, $J = 7.5$, 10.2 Hz, 1H), 6.15 (s, 1H), 7.05 (ddd, $J = 1.0$, 6.9, 7.6 Hz, 1H), 7.11 (ddd, $J = 1.0$, 6.9, 7.9 Hz, 1H), 7.22 (d, $J = 7.9$ Hz, 1H), 7.54 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 27.76 (t), 44.70 (d), 46.72 (t), 65.48 (t), 93.20 (d), 109.74 (d), 119.60 (d), 120.68 (d), 133.14 (s), 133.48 (s), 143.67 (s); IR (Nujol) 3370 cm^{-1}; MS *m*/*z* 187 (M^+). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.93; H, 6.85; N, 7.60. The second fraction gave 23 mg (36%) of (−)-(2*R*,3*S*)-3-amino-2,3-dihydro-1*H*-pyrrolo-[1,2-*a*]indolo-2-methanol (**14a**): oil; $[\alpha]_D = -14.5$ ($c = 0.15$, $CHCl_3$).

A mixture of (−)-**21a** (12 mg, 0.064 mmol), Mosher's (*R*)-acid chloride (19 mg, 0.075 mmol), and pyridine (20μL) in CH_2Cl_2 (2 mL) was stirred at room temperature for 24 h. Evaporation of the solvent gave the crude ester: ^1H NMR (δ, $CDCl_3$, 300 MHz) 2.76 (dd, $J = 5.8$, 16.2 Hz, 1H), 3.12 (dd, $J = 8.3$, 16.2 Hz, 1H), 3.30−3.39 (m, 1H), 3.50 (s, 3H), 3.77 (dd, $J = 5.5$, 10.3 Hz, 1H), 4.10 (dd, $J = 7.7$, 10.3 Hz, 1H), 4.31 (dd, $J = 7.9$, 11.0 Hz, 1H), 4.51 (dd, $J = 6.1$, 11.0 Hz, 1H), 6.12 (s, 1H),6.99−7.15 (overlapping, 3H), 7.29−7.51 (overlapping, 6H); ee >97%; MS *m*/*z* 403 (M^+).

Hydrogenation of 20a without HCl. According to the procedure described in the preceding preparation, compound **20a** (93 mg, 0.31 mmol) gave 8 mg (14%) of (+)-(2*S*)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indolo-2-methanol (**21a**), $[\alpha]_D = +2.9$ ($c = 0.12$, $CHCl_3$), and 28 mg (44%) of (+)−(2*S*,3*R*)-3-amino-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indolo-2-methanol (**14a**), $[\alpha]_D = +13.9$ ($c = 0.10$, $CHCl_3$).

Hydrogenation of 19a in the Presence of HCl. A mixture of 10% Pd/C (87 mg) and **19a** (107 mg, 0.35 mmol) in a 0.04 N solution of HCl in MeOH (8 mL) was stirred under H_2 for 24 h. After filtration through Celite, the solvent was removed under reduced pressure. The residue was treated with KOH and extracted with CH_2Cl_2. After evaporation of the solvent, the crude product was chromatographed on silica with AcOEt as eluent. The first fraction gave 15 mg (23%) of (−)-**21a.** The second fraction contained 10 mg (15%) of (+)−(3a*R*,2*R*)-2,3,3a,4-tetrahydro-1*H*-pyrrolo[1,2-*a*]indolo-2-methanol (**22**): oil; $[\alpha]_D = +47.9$ ($c = 0.11$, $CHCl_3$); ^1H NMR (δ, $CDCl_3$, 300 MHz) 1.13 (ddd, $J = 10.8$, 10.8, 11.4 Hz, 1H), 1.68 (br s, 1H, missing after deuteriation), 2.00 (ddd, $J = 5.9$, 6.1, 11.4 Hz, 1H), 2.50−2.64 (m, 1H), 2.88−2.99 (overlapping, 2H), 3.17 (dd, $J = 9.4$, 16.1 Hz, 1H), 3.53 (d, $J = 6.7$ Hz, 2H), 3.59 (dd, $J = 8.2$, 10.8 Hz, 1H), 3.96−4.09 (m, 1H), 6.56 (d, $J = 7.7$ Hz, 1H), 6.74 (dd, $J = 7.1$, 7.7 Hz, 1H), 7.04−7.12 (overlapping, 2H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 34.09 (t), 35.28 (t), 43.83 (d), 55.56 (t), 65.94 (d), 66.13 (t), 111.14 (d), 119.74 (d), 125.40 (d), 128.08 (d), 129.71 (s), 134.54 (s); IR (Nujol) 3340 cm^{-1}; MS *m*/*z* 189 (M^+). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.01; H, 8.12; N, 7.31. The third fraction gave 15 mg (21%) of (−)-**14a**.

Hydrogenation of 20a in the Presence of HCl. According to the procedure described in the preceding preparation, compound **20a** (108 mg, 0.35 mmol) gave 8 mg (12%) of (+)-(2*S*)-(**21a**), 14 mg (21%) of (−)-(3a*S*,2*S*)-2,3,3a,4-tetrahydro-1*H*-pyrrolo[1,2-*a*]indolo-2-methanol (**22**), $[\alpha]_D = -46.2$ ($c = 0.10$, $CHCl_3$), and 15 mg (21%) of (+)-**14a**.

Hydrogenation of 19b. A mixture of 10% $Pd(OH)_2$/C (70 mg) and **19b** (100 mg, 0.26 mmol) in MeOH (10 mL) was stirred under H_2 for 24 h. After filtration through Celite, the solvent was removed under reduced pressure and the crude product was chromatographed on silica with AcOEt/light petroleum (1/1) as eluent. The first fraction gave 10 mg (14%) of (−)-(α*S*,2*R*)-2-(α-hydroxybenzyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (**21b**): oil; $[\alpha]_D = -19.5$ ($c = 0.08$, $CHCl_3$); ^1H NMR (δ, $CDCl_3$, 300 MHz) 2.01 (br s, 1H, missing after deuteriation),3.11−3.28 (overlapping, 2H), 3.33−3.44 (m, 1H), 3.71 (dd, $J = 6.9$, 10.3 Hz, 1H), 3.89 (dd, $J = 8.1$, 10.3 Hz, 1H), 4.73 (d, $J = 8.3$ Hz, 1H), 6.15 (s, 1H), 6.99−7.13 (overlapping, 3H), 7.32−7.42 (overlapping, 5H), 7.51 (dd, $J = 2.4$, 6.7 Hz, 1H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 27.9 (t), 46.1 (t), 49.6 (d), 76.7 (d), 92.7(d), 105.3 (s), 109.2 (d), 119.2 (d),120.1 (d), 120.3 (d),-125.8 (s), 126.5 (d), 128.4 (d), 128.9 (d), 132.1 (s), 140.2(s); MS *m*/*z* 263 (M^+). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.94; H, 6.39; N, 5.51. The second fraction contained 31 mg (42%) of of (+)−(α*S*,2*S*,3*S*)-1-amino-2-(α-hydroxybenzyl)-2,3-dihydro-1*H*-pirrolo[1,2-*a*]indolo (**14b**): oil; $[\alpha]_D = +19.2$ ($c = 0.16$, $CHCl_3$); ee >97%.

A mixture of (−)-**21b** (6 mg, 0.023 mmol), Mosher's (*R*)-acid chloride (7 mg, 0.028 mmol), and pyridine (10μL) in CH_2Cl_2 (1

mL) was stirred at room temperature for 24 h. Evaporation of the solvent gave the crude ester: ^{1}H NMR (δ, $CDCl_3$, 300 MHz) 3.12 (d, J = 7.6 Hz, 2H),3.29−3.45 (m, 1H), 3.60 (s, 3H), 3.74 (dd, J = 6.9, 10.2 Hz, 1H), 3.90 (dd, J = 8.1, 10.2 Hz, 1H),4.76 (d, J = 8.1 Hz, 1H), 6.13 (s, 1H),7.00−7.11 (overlapping, 3H), 7.31−7.51 (overlapping, 11H); ee >97%; MS m/z 479 (M^+).

Hydrogenation of 20b. According to the procedure described in the preceding preparation, compound **20b** (100 mg, 0.26 mmol) gave 11 mg (15%) of (+)−(α*R*,2*S*)-2-(α-hydroxybenzyl)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole (**21b**), $[\alpha]_D = +18.1$ (c = 0.10, $CHCl_3$), and 29 mg (40%) of of (−)-(α*R*,2*R*,3*R*)-1-amino-2-(α-hydroxybenzyl)-2,3-dihydro-1*H*-pirrolo[1,2-*a*]indolo (**14b**), $[\alpha]_D = -18.9$ (c = 0.10, $CHCl_3$).

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Supporting Information Available: X-ray crystallographic data and copies of ^{1}H and ^{13}C NMR spectra for compounds **3**, **4**, **9**−**14**, and **17**−**22** as well as of two-dimensional ^{1}H-NOESY NMR spectra for compound **22**.

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