A Valuable Approach to Enantiopure Partially Saturated Pyrrolo- and Indolo[1,2-*a*]indoles by Intramolecular Nitrone Cycloadditions to the Cyclohexene Ring

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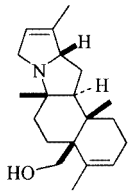
Enantiopure representatives of the title heterocyclic systems, which are of interest in alkaloid chemistry, are accessible by a procedure based upon intramolecular cycloadditions of nitrones derived from *N*-(cyclohex-2-enyl)-substituted pyrrole-2- and indole-2-carbaldehyde, followed by reductive manipulation of the cycloadducts.

Introduction

The synthetic potential of intramolecular nitrone cycloadditions is well documented and is currently exploited for a variety of targets, including heterocyclic and carbocyclic systems as well as open-chain multifunctional molecules.[1] The use of the cyclohexenyl moiety as the dipolarophilic site in intramolecular nitrone cycloadditions offers a few intrinsic advantages: (*i*) the formation at once of a tricyclic skeleton, and (*ii*) highly regio- and stereoselective outcomes, due to geometric restraints imposed by the poor rotational and torsional flexibility of the reactant. Extensive information on this topic is available in the literature.[2] In continuation of our research program in such fields,[2c][2d] we have developed a valuable procedure affording enantiopure, partially saturated pyrrolo- and indolo[1,2-*a*]indoles. Both these systems are of interest, in being related to diterpenoidal alkaloids such as thelepogine (**1**)[3] and polyavolensin (**2**).[4]



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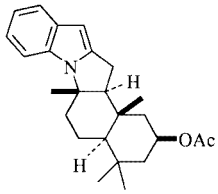

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The construction of the pyrrolo[1,2-*a*]indole skeleton has been reported by several authors,[5] principally by means of radical cyclization methodology,[5d–5l] but the synthesis of optically active derivatives is still rare.[5f][5h] On the other hand, no synthetic approach, to the best of our knowledge, is available for the indolo[1,2-*a*]indole skeleton.

Results and Discussion

As suitable and readily accessible substrates for our purpose, we planned to use nitrone species deriving from the hitherto unknown *N*-(cyclohex-2-enyl)-substituted pyrrole-2- and indole-2-carbaldehyde (**3a** and **3b**), the synthesis of which is outlined in Scheme 1. At first, we tested the behaviour of these aldehydes with the commercially available benzylhydroxylamine. As shown in Scheme 2, the reactions in both cases furnished one cycloadduct, by way of the transient nitrones **4**. X-ray analysis established the structure **5a** with a *cis* relationship between all hydrogen atoms in stereogenic positions (Figure 1). In the light of the close correspondence of the NMR spectroscopic data of **5b** and **5a**, we felt confident in assigning the same relative configuration to both cycloadducts. The stereochemical outcome of the cycloaddition may be interpreted by considering that (*i*) the (*Z*) configuration of the nitrone is the most suitable for

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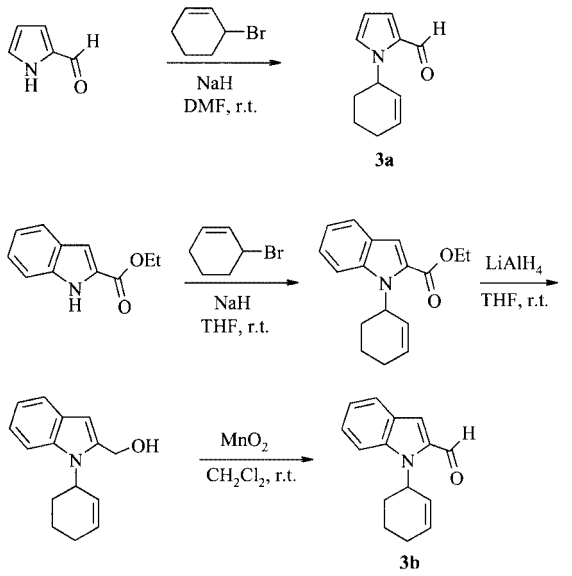
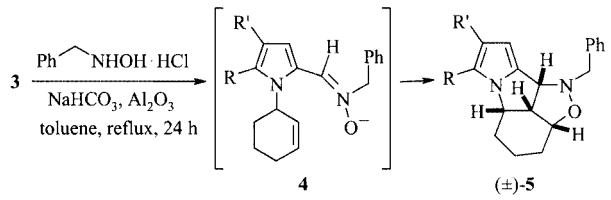
intramolecular reaction, and (*ii*) the dipole can only attack the face of the cyclohexenyl ring folded towards the pyrrole nucleus.



Scheme 1. Synthesis of *N*-(cyclohex-2-enyl)pyrrole-2-carbaldehyde (**3a**) and *N*-(cyclohexy-2-enyl)indole-2-carbaldehyde (**3b**)



Entry	R	R'	Yield (%)
a	H	H	55
b	-(CH=CH)$_2$-		88

Scheme 2. Generation and intramolecular cycloaddition of nitrones **4a**, **4b**

At this point, we treated the same aldehydes with an enantiopure hydroxylamine, the benzyl-like and reasonably inexpensive (*R*)-(1-phenylethyl)hydroxylamine (Scheme 3). The initially formed nitrones **6** evolved spontaneously to give two diastereoisomeric cycloadducts **7** and **8**, which were isolated in the pure state by chromatographic separation.[6] X-ray analysis of compound **7a** (Figure 1) allowed both its relative and absolute configurations to be determined, as the absolute stereochemistry of the starting hydroxylamine was known. The configuration of the corresponding diastereoisomer **8a** was thus indirectly established. Once again, the similarity of the NMR spectroscopic data served for the stereochemical assignment of the indole cycloadducts **7b** and **8b**. It is to be noted that the intramolecular cycloaddition of nitrones **6** took place with total control over the relative configurations of the new stereocentres, while their absolute configurations were influenced to a small extent by the enantiopure nitrone moiety.

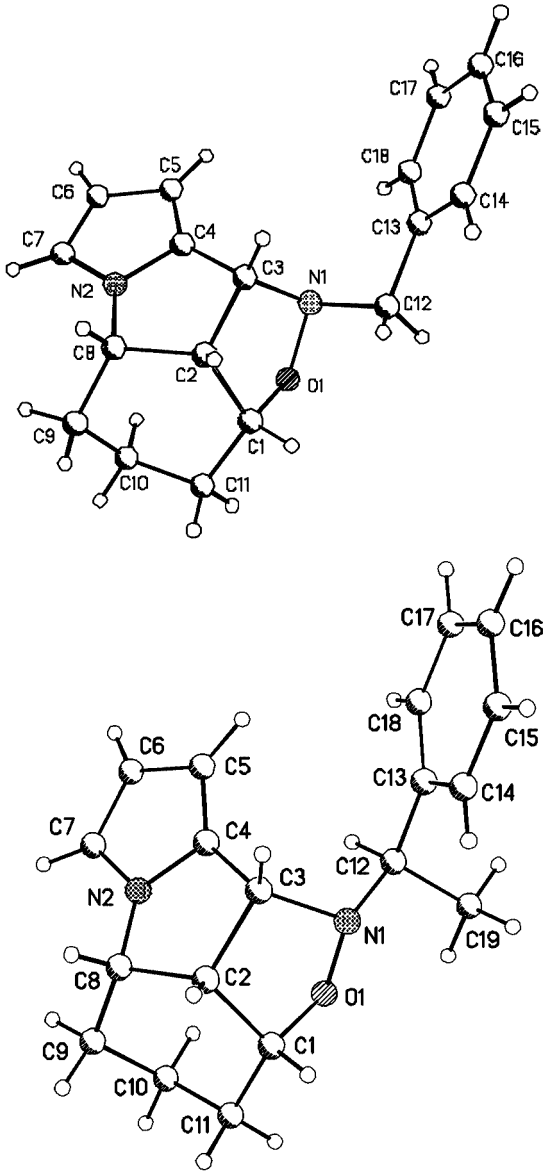
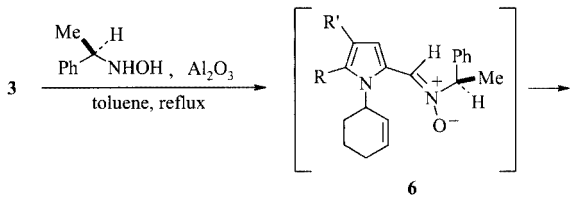


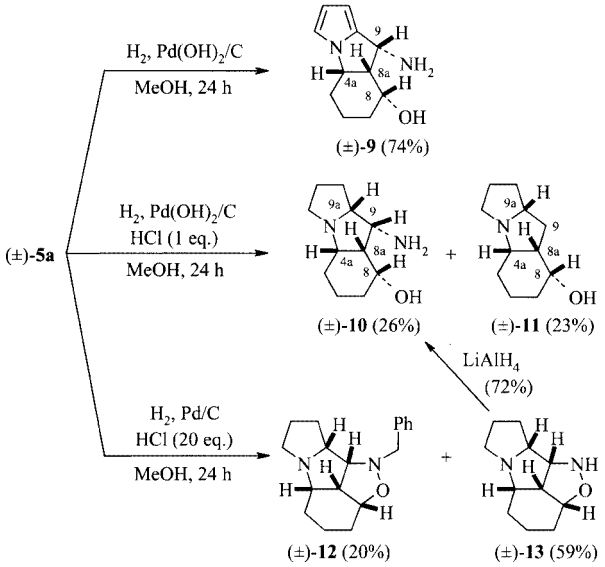
Figure 1. X-ray crystal structures of cycloadducts **5a** (top) and **7a** (bottom), showing the atomic numbering scheme; note that the stereochemistry of the pyramidal N1 atoms is different in the two molecules

As the next stage of our work, we manipulated the above cycloadducts with the aim of transforming them into partially saturated, functionalised pyrrolo- and indolo[1,2-*a*]indoles. We chose catalytic hydrogenation, having in mind (*i*) the unmasking of the latent functionalities of the isoxazolidine ring and (*ii*) the removal of the benzyl pendant. Experimental conditions were checked by use of the racemic cycloadduct **5a**, and were found subtle in order to achieve a chemoselective reaction (Scheme 4). The presence of a strong protic acid usefully determined the saturation of the pyrrole nucleus, but at the same time it favoured the hydrogenolytic loss of the pseudobenzylic amino group. Significantly, when a large quantity of HCl was used, saturation of the pyrrole was very fast in comparison with the cleavage of the isoxazolidine ring, so that the tetracyclic compound



Entry	R	R'	Yield (%) 7	8
a	H	H	22	24
b	-(CH=CH)$_2$-		50	35

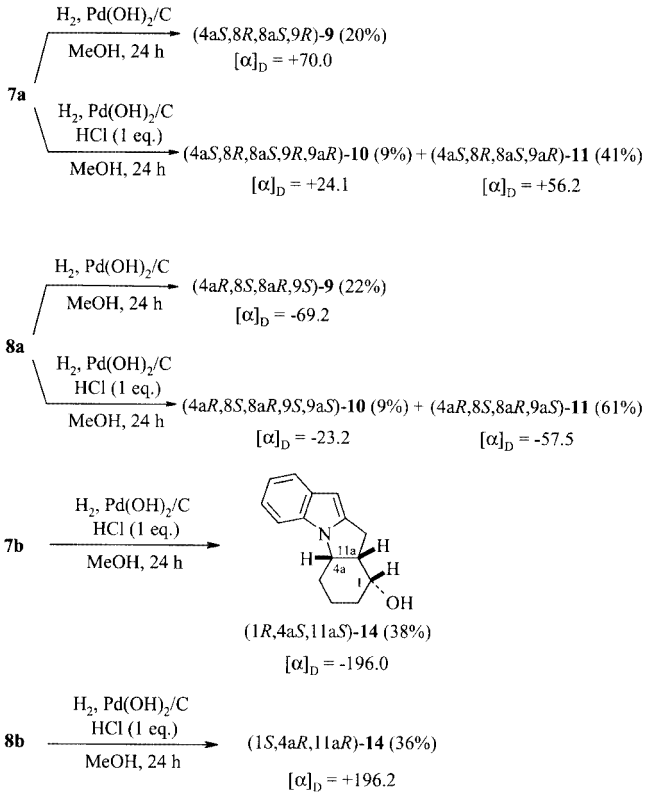
Scheme 3. Generation and intramolecular cycloaddition of nitrones **6a**, **6b**



Scheme 4. Hydrogenation reactions of cycloadduct **5a**

13 was the major product together with its precursor **12**. However, the subsequent reduction of **13** with $LiAlH_4$ gave the interesting amino alcohol **10** in good yield. The unique configuration of the new stereogenic carbon atom formed in the hydrogenation (in the 9a position) constitutes a noteworthy feature. The actual stereochemistry was elucidated by submitting compounds **10** and **11** to exhaustive two-dimensional NMR analysis in the form of homo- and heteronuclear correlations, which allowed the identification of the signals of the various protons. Hence, a *cis* disposition between 9a-H and 9-H in compound **10** was deduced from coupling constants and NOESY measurements.

Finally, the hydrogenation procedures just described were applied to the optically active cycloadducts **7a**, **7b**, **8a**, and



Scheme 5. Hydrogenation reactions of optically active cycloadducts

8b. As illustrated in Scheme 5, this enabled us to acquire both enantiomers of hexahydro-4a*H*-pyrrolo[1,2-*a*]indole **9**, decahydro-1*H*-pyrrolo[1,2-*a*]indoles **10** and **11**, and hexahydro-1*H*-indolo[1,2-*a*]indole **14**.

Conclusion

In conclusion, the work described here has furnished a number of enantiopure representatives of the title heterocyclic systems and may represent a promising step for a future synthetic approach to alkaloid-like unnatural compounds.

Experimental Section

General Remarks: Preparative column chromatography was carried out on silica gel 60 (Merck) (mesh size 63−200 μm). NMR spectra were recorded with an AC 300 Bruker instrument. Chemical shifts 'are reported in ppm relative to $CHCl_3$ (δ^1H '= 7.26 ppm) and $CDCl_3$ (δ^{13}C '= 77.0 ppm) as internal standards. Optical rotations were measured with a Perkin−Elmer 241 polarimeter. Mass spectra were determined with a WG-70EQ instrument. IR spectra were taken with a Perkin−Elmer 1725X FT-IR spectrophotometer. Melting points were measured with a Büchi B-540 heating unit and are not corrected.

***N*-(Cyclohex-2-enyl)pyrrole-2-carbaldehyde (3a):** 3-Bromocyclohexene (0.95 g, 6.0 mmol) was added to a suspension of pyrrole-2-carbaldehyde (0.56 g, 5.9 mmol) and NaH (0.45 g, 18.7 mmol) in anhydrous DMF (16 mL). The mixture was stirred at room temperature for 2 h and then treated with 5% aqueous $NaHCO_3$ (25 mL).

The suspension was extracted with Et_2O; the organic layer was dried with Na_2SO_4, and the solvents were evaporated under reduced pressure. The residue was chromatographed on a silica gel column with light petroleum ether/EtOAc/CH_2Cl_2 (3:1:1) as eluent to give **3a** (0.64 g, 62%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55−1.77 (m, 3 H), 1.98−2.18 (m, 3 H), 5.60−5.77 (2 H, overlapping), 6.09 (dt, *J* = 3.6, 7.9 Hz, 1 H), 6.20 (dd, *J* = 2.6, 4.0 Hz, 1 H), 6.95 (dd, *J* = 1.8, 4.0 Hz, 1 H), 7.13 (dd, *J* = 1.8, 2.6 Hz, 1 H), 9.55 (s, 1 H) ppm. MS: *m*/*z* = 175 [M$^+$]. IR: ṽ = 1740 cm^{-1}. $C_{11}H_{13}NO$ (175.23): calcd. C 75.40, H 7.48, N 7.99; found C 75.45, H 7.63, N 8.11.

***N*-(Cyclohex-2-enyl)-2-(hydroxymethyl)indole:** Ethyl indole-2-carboxylate (1.72 g, 9.1 mmol) was added portionwise, under nitrogen, to a suspension of NaH (0.43 g, 18.0 mmol) in THF (20 mL). After 5 min, 3-bromocyclohexene (1.49 mL, 9.1 mmol) was added dropwise and the mixture was stirred at room temperature for 18 h. MeOH (10 mL) was added and the resulting solvents were evaporated to dryness. The residue was taken up in water (10 mL) and adjusted to pH = 7 with HCl (1 N). The mixture was extracted with $CHCl_3$, the organic layer was dried with Na_2SO_4, and the solvents were evaporated under reduced pressure. The residue was chromatographed on a silica gel column with light petroleum ether/Et_2O (5:1) as eluent. The first fraction gave a crude product (2.00 g, 7.4 mmol), which was dissolved in THF (10 mL) and added to $LiAlH_4$ (1.11 g, 29.0 mmol) in THF (10 mL), cooled at 0 °C. The suspension was stirred at room temperature for 3 h. MeOH (10 mL) was added dropwise and the solvents were evaporated to dryness. The residue was taken up in water (10 mL) and adjusted to pH = 7 with HCl (1 N). The suspension was extracted with CH_2Cl_2, the organic layer was dried with Na_2SO_4, and the solvents were evaporated under reduced pressure. The residue was chromatographed on a silica gel column with CH_2Cl_2 as eluent to give the title compound (1.36 g, 66% from ethyl indole-2-carboxylate). M.p. 168−169 °C (from diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.67−2.31 (m, 7 H, 6 H after deuteration), 4.78 (s, 2 H), 5.17−5.29 (m, 1 H), 5.81−5.91 (m, 1 H), 5.98−6.06 (m, 1 H), 6.43 (s, 1 H), 7.01−7.17 (m, 2 H), 7.50−7.61 (m, 2 H) ppm. MS: *m*/*z* = 227 [M$^+$]. IR: ṽ = 3380 cm^{-1}. $C_{15}H_{17}NO$ (227.31): calcd. C 79.26, H 7.54, N 6.16; found C 79.09, H 7.72, N 5.99.

***N*-(Cyclohex-2-enyl)indole-2-carbaldehyde (3b):** Activated MnO_2 (1.2 g, 13 mmol) was added to a solution of *N*-(cyclohex-2-enyl)-2-(hydroxymethyl)indole (0.30 g, 1.3 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 18 h and filtered through a short path of Celite, which was subsequently washed several times with CH_2Cl_2. The filtrate was concentrated, and the residue was chromatographed on a silica gel column with light petroleum ether/Et_2O (1:1) as eluent to give **3b** (0.14 g, 48%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78−2.29 (m, 6 H), 5.83 (dd, *J* = 2.1, 10.0 Hz, 1 H), 5.95−6.04 (m, 1 H), 6.23−6.33 (m, 1 H), 7.13 (dd, *J* = 7.9, 7.9 Hz, 1 H), 7.25 (s, 1 H), 7.30 (dd, *J* = 7.9, 8.2 Hz, 1 H), 7.67 (d, *J* = 8.2 Hz, 1 H), 7.72 (d, *J* = 7.9 Hz, 1 H), 9.87 (s, 1 H) ppm. MS: *m*/*z* = 225 [M$^+$]. IR: ṽ = 1740 cm^{-1}. $C_{15}H_{15}NO$ (225.29): calcd. C 79.97, H 6.71, N 6.22; found C 8.05, H 6.52, N 6.30.

General Procedure for the Treatment of Aldehydes 3a and 3b with Benzylhydroxylamine: A suspension of *N*-benzylhydroxylamine hydrochloride (4.0 mmol), Al_2O_3 (4.0 g) and $NaHCO_3$ (4.0 mmol) in toluene (105 mL) was stirred at room temperature for 1 h. A solution of **3** (3.4 mmol) in toluene (20 mL) was added, and the resulting mixture was heated under reflux whilst stirring for 24 h. After filtration and evaporation of the solvent under reduced pressure, the residue was chromatographed on a silica gel column with light petroleum ether/EtOAc (3:1) as eluent to give **5**.

(2a*R,5a*S**,9b*R**,9c*R**)-1-Benzyl-1,2a,3,4,5,5a,9b,9c-octahydroisoxazolo[3,4,5-*c*,*d*]pyrrolo[1,2-*a*]indole (5a):** Yield: 55%. M.p. 129−131 °C (from hexane/benzene). ^{1}H NMR (300 MHz, $CDCl_3$, −40 °C): major conformer: δ = 1.29−1.40 (m, 2 H), 1.61−1.81 (m, 2 H), 1.99−2.10 (m, 1 H), 2.28−2.42 (m, 1 H), 3.64 (ddd, *J* = 6.5, 6.5, 7.5 Hz, 1 H), 3.94 (d, *J* = 12.4 Hz, 1 H), 4.17 (d, *J* = 12.4 Hz, 1 H), 4.32−4.39 (m, 1 H), 4.51−4.59 (m, 1 H), 4.75 (d, *J* = 7.5 Hz, 1 H), 5.90−5.92 (m, 1 H), 6.26−6.29 (m, 1 H), 6.51−6.53 (m, 1 H), 7.26−7.49 (m, 5 H); minor conformer: 1.15−1.28 (m, 2 H), 1.51−1.81 (m, 2 H), 1.99−2.10 (m, 1 H), 2.28−2.42 (m, 1 H), 3.57 (ddd, *J* = 6.5, 6.5, 7.5 Hz, 1 H), 4.05−4.25 (3 H, overlapping), 4.26−4.53 (m, 1 H), 4.97 (d, *J* = 7.5 Hz, 1 H), 6.01−6.05 (m, 1 H), 6.33−6.37 (m, 1 H), 6.67−6.69 (m, 1 H), 7.26−7.49 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, −40 °C): major conformer: δ '= 13.3 (t), 26.2 (t), 27.9 (t), 49.5 (d), 53.4 (d), 59.3 (t), 68.2 (d), 71.9 (d), 101.7 (d), 113.2 (d), 114.0 (d), 120.0 (d), 128.4 (d), 128.6 (d), 137.0 (s), 137.1 (s); minor conformer: 14.0 (t), 26.3 (t), 27.8 (t), 50.3 (d), 53.4 (d), 56.2 (t), 67.2 (d), 74.3 (d), 103.2 (d), 112.0 (d), 113.3 (d), 127.8 (d), 128.4 (d), 128.6 (d), 132.1 (s), 137.8 (s) ppm. MS: *m*/*z* = 280 [M$^+$]. $C_{18}H_{20}N_2O$ (280.37): calcd. C 77.11, H 7.19, N 9.99; found C 76.95, H 7.28, N 9.81.

(2a*R,5a*S**,11b*R**,11c*R**)-1-Benzyl-1,2a,3,4,5,5a,11b,11c-octahydroindolo[1,2-*a*]isoxazolo[3,4,5-*c*,*d*]indole (5b):** Yield: 88%. M.p. 129−130 °C (from pentane/diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.64−1.83 (4 H, overlapping), 2.09 (m, 1 H), 2.92 (1 H, br d, *J* = 14.6 Hz), 3.70 (ddd, *J* = 7.7, 7.7, 7.7 Hz, 1 H), 4.02−4.19 (m, 1 H), 4.29 (d, *J* = 13.2 Hz, 1 H), 4.35−4.55 (m, 1 H), 4.58−4.63 (m, 1 H), 4.83−4.98 (m, 1 H), 6.31 (s, 1 H), 7.04−7.14 (m, 2 H), 7.26−7.62 (m, 7 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ '= 14.4 (t), 26.9 (t), 27.9 (t), 50.4 (d), 54.7 (d), 59.6 (t), 68.0 (d), 73.6 (d), 95.8 (d), 110.5 (d), 120.2 (d), 121.1 (d), 121.7 (d), 128.0 (d), 128.8 (d), 129.5 (d), 133.4 (s), 134.8 (s), 138.1 (s) ppm. MS: *m*/*z* = 330 [M$^+$]. $C_{22}H_{22}N_2O$ (330.43): calcd. C 79.97, H 6.71, N 8.48; found C 79.89, H 6.90, N 8.61.

General Procedure for the Treatment of Aldehydes 3a and 3b with (*R*)-*N*-(α-Methylbenzyl)hydroxylamine: A suspension of (*R*)-*N*-(α-methylbenzyl)hydroxylamine[7] (5.8 mmol), **3** (5.8 mmol), and Al_2O_3 (6.5 g) in toluene (150 mL) was heated under reflux for 24 h. After filtration and evaporation of the solvent under reduced pressure, the residue was chromatographed on a silica gel column with light petroleum ether/EtOAc (3:1) as eluent to give **7** and **8**.

(−)-(α*R*,2a*R*,5a*S*,9b*R*,9c*R*)-1-(α-Methylbenzyl)-1,2a,3,4,5,5a,9b,9c-octahydroisoxazolo[3,4,5-*c*,*d*]pyrrolo[1,2-*a*]indole (7a): Yield: 22%. M.p. 120−121 °C (hexane/benzene). ^{1}H NMR (300 MHz, $CDCl_3$, −40 °C): major conformer: δ = 1.45 (d, *J* = 6.3 Hz, 3 H), 1.55−1.78 (m, 4 H), 2.16−2.31 (m, 1 H), 2.37−2.44 (m, 1 H), 3.60 (ddd, *J* = 7.5, 7.5, 7.5 Hz, 1 H), 4.21−4.39 (3 H, overlapping), 4.88 (d, *J* = 7.5 Hz, 1 H), 5.99 (br. s, 1 H), 6.38 (dd, *J* = 3.1, 3.1 Hz, 1 H), 6.70 (br. s, 1 H), 7.25 (dd, *J* = 7.3, 7.3 Hz, 1 H), 7.34 (dd, *J* = 7.3, 7.5 Hz, 2 H), 7.46 (d, *J* = 7.5 Hz, 2 H); minor conformer: 1.45 (d, *J* = 6.3 Hz, 3 H), 1.55−1.78 (4 H, overlapping), 2.37−2.44 (2 H, overlapping), 3.69 (ddd, *J* = 7.5, 7.5, 7.5 Hz, 1 H), 4.08 (q, *J* = 6.3 Hz, 1 H), 4.21−4.39 (m, 1 H), 4.41−4.47 (m, 1 H), 5.17 (d, *J* = 7.5 Hz, 1 H), 6.18 (br. s, 1 H), 6.42 (dd, *J* = 3.1, 3.1 Hz, 1 H), 6.62 (br. s, 1 H), 7.25 (dd, *J* = 7.3, 7.3 Hz, 1 H), 7.34 (dd, *J* = 7.3, 7.5 Hz, 2 H), 7.46 (d, *J* = 7.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, −30 °C): major conformer: δ '= 13.2 (t), 24.4 (q), 25.9 (t), 26.9 (t), 50.0 (d), 52.8 (d), 60.6 (d), 64.1 (d), 73.1 (d), 102.7 (d), 112.3 (d), 112.4 (d), 126.7 (d), 128.3 (d), 131.5 (s), 142.9 (s); minor

conformer: 12.6 (t), 22.6 (q), 25.4 (t), 27.4 (t), 48.4 (d), 53.0 (d), 61.4 (d), 66.3 (d), 70.7 (d), 99.7 (d), 111.2 (d), 113.3 (d), 126.7 (d), 128.0 (d), 136.6 (s), 142.7 (s) ppm. MS: *m*/*z* = 294 [M$^+$]. [α]$_D^{22}$ = −10.0 (*c* = 0.31, $CHCl_3$). $C_{19}H_{22}N_2O$ (294.40): calcd. C 77.52, H 7.53, N 9.52; found C 77.40, H 7.58, N 9.71.

(+)-(α*R*,2a*S*,5a*R*,9b*S*,9c*S*)-1-(α-Methylbenzyl)-1,2a,3,4,5,5a,9b,9c-octahydroisoxazolo[3,4,5-*c*,*d*]pyrrolo[1,2-*a*]indole (8a): Yield: 24%. M.p. 172−173 °C (hexane/benzene). ^{1}H NMR (300 MHz, $CDCl_3$, −40 °C): major conformer: δ = 1.27−1.38 (m, 2 H), 1.46 (d, *J* = 6.4 Hz, 3 H), 1.60−1.75 (m, 2 H), 2.07−2.17 (m, 1 H), 2.30−2.39 (m, 1 H), 3.56 (ddd, *J* = 7.6, 7.6, 7.6 Hz, 1 H), 3.97 (q, *J* = 6.4 Hz, 1 H), 4.22−4.36 (m, 1 H), 4.39−4.48 (m, 1 H), 4.66 (d, *J* = 7.6 Hz, 1 H), 5.89 (br. s, 1 H), 6.27 (br. s, 1 H), 6.51 (br. s, 1 H), 7.25 (dd, *J* = 7.3, 7.3 Hz, 1 H), 7.34 (dd, *J* = 7.3, 7.4 Hz, 2 H), 7.44 (d, *J* = 7.4 Hz, 2 H); minor conformer: 1.27−1.38 (m, 2 H), 1.46 (d, *J* = 6.4 Hz, 3 H), 1.60−1.75 (m, 2 H), 1.91−2.04 (m, 1 H), 2.30−2.39 (m, 1 H), 3.60 (ddd, *J* = 7.6, 7.6, 7.6 Hz, 1 H), 4.16 (q, *J* = 6.4 Hz, 1 H), 4.22−4.36 (m, 1 H), 4.39−4.48 (m, 1 H), 5.12 (d, *J* = 7.6 Hz, 1 H), 6.13 (br. s, 1 H), 6.39 (br. s, 1 H), 6.70 (br. s, 1 H), 7.25 (dd, *J* = 7.3, 7.3 Hz, 1 H), 7.34 (dd, *J* = 7.3, 7.4 Hz, 2 H), 7.44 (d, *J* = 7.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, −30 °C): major conformer: δ '= 12.9 (t), 21.9 (q), 25.9 (t), 27.7 (t), 48.3 (d), 53.2 (d), 62.0 (d), 67.3 (d), 71.4 (d), 99.4 (d), 111.1 (d), 113.3 (d), 127.3 (d), 128.6 (d), 136.4 (s), 143.4 (s); minor conformer: 13.1 (t), 22.2 (q), 25.9 (t), 27.5 (t), 49.9 (d), 53.2 (d), 60.5 (d), 64.6 (d), 73.2 (d), 102.2 (d), 111.1 (d), 111.7 (d), 126.1 (d), 127.5 (d), 136.4 (s), 143.4 (s). MS: *m*/*z* = 294 [M$^+$]. [α]$_D^{22}$ = +24.0 (*c* = 0.29, $CHCl_3$). $C_{19}H_{22}N_2O$ (294.40): calcd. C 77.52, H 7.53, N 9.52; found C 77.50, H 7.38, N 9.55.

(+)-(α*R*,2a*R*,5a*S*,11b*R*,11c*R*)-1-(α-Methylbenzyl)-1,2a,3,4,5,5a,11b,11c-octahydroindolo[1,2-*a*]isoxazolo[3,4,5-*c*,*d*]indole (7b): Yield: 50%. M.p. 123−125 °C (pentane/diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$, −40 °C): major conformer: δ = 1.30−1.44 (m, 2 H), 1.46 (d, *J* = 6.2 Hz, 3 H), 1.60−1.84 (m, 2 H), 2.11−2.27 (m, 1 H), 2.81−3.02 (m, 1 H), 3.62 (ddd, *J* = 7.6, 7.6, 7.6 Hz, 1 H), 4.22−4.36 (2 H, overlapping), 4.39−4.49 (m, 1 H), 4.92 (d, *J* = 7.6 Hz, 1 H), 6.17 (s, 1 H), 7.01−7.14 (m, 2 H), 7.25−7.31 (m, 1 H), 7.35−7.57 (m, 4 H), 7.59−7.67 (m, 2 H); minor conformer: 1.30−1.44 (m, 2 H), 1.55 (d, *J* = 6.2 Hz, 3 H), 1.60−1.84 (m, 2 H), 2.11−2.27 (m, 1 H), 2.81−3.02 (m, 1 H), 3.76 (ddd, *J* = 7.6, 7.6, 7.6 Hz, 1 H), 4.06 (q, *J* = 6.2 Hz, 1 H), 4.22−4.36 (m, 1 H), 4.65−4.75 (m, 1 H), 5.23 (d, *J* = 7.6 Hz, 1 H), 6.44 (s, 1 H), 7.01−7.14 (m, 2 H), 7.25−7.31 (m, 1 H), 7.35−7.57 (m, 4 H), 7.59−7.67 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ '= 13.7 (t), 23.8 (q), 26.2 (t), 27.2 (t), 50.5 (d), 54.0(d), 61.5 (d), 64.9 (d), 73.0 (d), 109.9 (d), 119.5 (d), 120.5 (d), 121.1 (d), 126.0 (d), 127.2 (d), 128.5 (d), 129.2 (d), 132.8 (s), 133.9 (s), 143.3 (s), 156.0 (s) ppm. MS: *m*/*z* = 344 [M$^+$]. [α]$_D^{22}$ = +99.5 (*c* = 0.17, $CHCl_3$). $C_{23}H_{24}N_2O$ (344.46): calcd. C 80.20, H 7.02, N 8.13; found C 80.07, H 6.98, N 8.29.

(−)-(α*R*,2a*S*,5a*R*,11b*S*,11c*S*)-1-(α-Methylbenzyl)-1,2a,3,4,5,5a,11b,11c-octahydroindolo[1,2-*a*]isoxazolo[3,4,5-*c*,*d*]indole (8b): Yield: 35%. M.p. 202−204 °C (pentane/diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$, −40 °C): major conformer: δ = 1.26−1.41 (m, 2 H), 1.50 (d, *J* = 6.2 Hz, 3 H), 1.64−1.84 (m, 2 H), 2.03−2.21 (m, 1 H), 2.82−3.02 (m, 1 H), 3.66 (ddd, *J* = 7.8, 7.8, 7.8 Hz, 1 H), 4.03 (q, *J* = 6.2 Hz, 1 H), 4.43−4.52 (m, 1 H), 4.53−4.67 (m, 1 H), 4.78 (d, *J* = 7.8 Hz, 1 H), 6.24 (s, 1 H), 6.99−7.12 (m, 2 H), 7.25−7.44 (m, 4 H), 7.46−7.57 (m, 3 H); minor conformer: 1.26−1.41 (m, 2 H), 1.50 (d, *J* = 6.2 Hz, 3 H), 1.64−1.84 (m, 2 H), 1.89−2.05 (m, 1 H), 2.82−3.02 (m, 1 H), 3.66 (ddd, *J* = 7.8, 7.8, 7.8 Hz, 1 H), 4.28 (q, *J* = 6.2 Hz, 1 H), 4.43−4.52 (m, 1 H), 4.53−4.67 (m, 1 H), 5.23 (d, *J* = 7.8 Hz, 1 H), 6.52 (s, 1 H), 6.99−7.12 (m, 2 H), 7.25−7.44 (m, 4 H), 7.46−7.57 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ '= 13.4 (t), 22.0 (q), 26.0 (t), 27.0 (t), 49.0 (d), 53.9 (d), 62.4 (d), 66.9 (d), 72.2 (d), 109.8 (d), 119.3 (d), 120.2 (d), 121.2 (d), 127.6 (d), 128.7 (d), 131.4 (s), 134.1 (s), 143.6 (s), 154.5 (s) ppm. MS: *m*/*z* = 344 [M$^+$]. [α]$_D^{22}$ = −96.0 (*c* = 0.17, $CHCl_3$). $C_{23}H_{24}N_2O$ (344.46): calcd. C 80.20, H 7.02, N 8.13; found C 80.11, H 7.18, N 7.99.

Hydrogenation of 5a with Pd(OH)$_2$/C in MeOH: A mixture of Pd(OH)$_2$/C (10%, 45 mg) and **5a** (0.10 g, 0.36 mmol) in MeOH (15 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 CH_2Cl_2/MeOH (5:1) as eluent to give (4a*R**,8*S**,8a*R**,9*S**)-9-amino-5,6,7,8,8a,9-hexahydro-4a*H*-pyrrolo[1,2-*a*]indol-8-ol (**9**) (51 mg, 74%). M.p. 147−148 °C (from diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23−1.96 (5 H, overlapping), 2.11−2.18 (m, 1 H), 2.37 (br. s, 3 H, missing after deuteration), 3.12 (ddd, *J* = 6.9, 7.0, 7.4 Hz, 1 H), 4.04−4.20 (2 H, overlapping), 4.55 (d, *J* = 7.4 Hz, 1 H), 5.90 (dd, *J* = 1.5, 3.5 Hz, 1 H), 6.23 (dd, *J* = 2.5, 3.5 Hz, 1 H), 6.59 (dd, *J* = 1.5, 2.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ '= 18.7 (t), 31.4 (t), 33.5 (t), 48.3 (d), 51.5 (d), 57.0 (d), 68.6 (d), 98.8 (d), 112.0 (d), 112.7 (d), 140.0 (s) ppm. MS: *m*/*z* = 192 [M$^+$]. IR: ṽ = 3310, 3340, 3380 cm^{-1}. $C_{11}H_{16}N_2O$ (192.26): calcd. C 68.72, H 8.39, N 14.57; found C 68.86, H 8.45, N 14.67.

Hydrogenation of 5a with Pd(OH)$_2$/C and HCl (1 equiv.) in MeOH: A mixture of Pd/C (10%, 0.14 g) and **5a** (0.22 g, 0.78 mmol) in a solution of HCl in MeOH (0.02 N, 39 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 50% NaOH solution and extracted with CH_2Cl_2. After evaporation of the solvent, the crude product was chromatographed on silica gel with CH_2Cl_2/MeOH/NH_3 (7:2/1) as eluent. The first fraction gave (4a*R**,8*S**,8a*R**,9a*S**)-2,3,4a,5,6,7,8,8a,9,9a-decahydro-1*H*-pyrrolo-[1,2-*a*]indol-8-ol (**11**) (32 mg, 23%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98−1.57 (5 H, overlapping), 1.64−1.81 (3 H, overlapping), 1.83−2.03 (4 H, overlapping), 2.65−2.86 (2 H, overlapping), 2.92 (dt, *J* = 7.2, 10.3 Hz, 1 H), 3.09 (ddd, 1 H, *J* = 5.2, 5.2, 10.4 Hz), 3.40 (br. s, 1 H, missing after deuteration), 3.47−3.61 (m, 1 H), 3.89 (ddd, 1 H, *J* = 5.1, 5.1, 10.5 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ '= 21.4 (t), 25.5 (t), 28.7 (t), 28.9 (t), 29.7 (t), 32.9 (t), 45.6 (t), 48.8 (d), 60.1 (d), 65.4 (d), 69.5 (d) ppm. MS: *m*/*z* = 181 [M$^+$]. IR: ṽ = 3370 cm^{-1}. $C_{11}H_{19}NO$ (181.28): calcd. C 72.88, H 10.56, N 7.73; found C 73.06, H 10.41, N 7.90. The second fraction gave (4a*R**,8*S**,8a*R**,9*S**,9a*S**)-9-amino-2,3,4a,5,6,7,8,8a,9,9a-decahydro-1*H*-pyrrolo[1,2-*a*]indol-8-ol (**10**) (40 mg, 26%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20−1.33 (m, 1 H), 1.44−1.84 (7 H, overlapping), 1.87−2.06 (2 H, overlapping), 2.18 (dt, *J* = 6.5, 8.5 Hz, 1 H), 2.47 (dt, *J* = 5.9, 6.9 Hz, 1 H), 2.81 (dt, *J* = 5.5, 6.3 Hz, 1 H), 2.90−3.06 (2 H, overlapping), 3.14 (br. s, 3 H, missing after deuteration), 3.57 (dd, *J* = 7.2, 7.2 Hz, 1 H), 4.07 (ddd, *J* = 3.8, 5.2, 6.9 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8 (t), 22.8 (t), 26.1 (t), 27.6 (t), 32.1 (t), 45.7 (t), 49.5 (d), 51.8 (d), 59.5 (d), 67.4 (d), 71.6 (d) ppm. MS: *m*/*z* = 196 [M$^+$]. IR: ṽ = 3320, 3360, 3380 cm^{-1}. $C_{11}H_{20}N_2O$ (196.29): calcd. C 67.31, H 10.27, N 14.27; found C 67.30, H 10.42, N 14.47.

Hydrogenation of 5a with Pd(OH)$_2$/C and HCl (20 equiv.) in MeOH: A mixture of Pd/C (10%, 0.16 g) and **5a** (0.20 g, 0.71 mmol) in a solution of HCl in MeOH (0.5 N, 29 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 50% NaOH solution and extracted with CH_2Cl_2. After evaporation of the solvent, the

crude product was chromatographed on silica gel with CH_2Cl_2/MeOH/NH_3 (20:2/1) as eluent. The first fraction gave (2a*R**,5a*S**,9a*R**,9b*R**,9c*R**)-1-benzyl-1,2a,3,4,5,5a,7,8,9,9a,9b,9c-dodecahydroisoxazolo[3,4,5-*c*,*d*]pyrrolo[1,2-*a*]indole (**12**): (40 mg, 20%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07−1.33 (3 H, overlapping), 1.42−1.55 (2 H, overlapping), 1.61−1.74 (2 H, overlapping), 1.90−2.05 (3 H, overlapping), 2.08−2.22 (3 H, overlapping), 2.41−2.51 (m, 1 H), 2.81 (br. s, 1 H), 3.34−3.42 (m, 1 H), 3.82, 3.88 (AB, 2 H, *J* = 14.0 Hz), 4.05 (br. s, 1 H), 7.17−7.41 (m, 5 H) ppm. MS: *m*/*z* = 284 [M$^+$]. $C_{18}H_{24}N_2O$ (284.40): calcd. C 76.02, H 8.51, N 9.85; found C 75.90, H 8.59, N 7.69. The second fraction gave (2a*R**,5a*S**,9a*R**,9b*R**,9c*R**)-1,2a,3,4,5,5a,7,8,9,9a,9b,9c-dodecahydroisoxazolo[3,4,5-*c*,*d*]pyrrolo[1,2-*a*]indole (**13**): (81 mg, 59%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19−1.29 (m, 1 H), 1.38−2.01 (8 H, overlapping), 2.16−2.22 (2 H, overlapping), 2.27−2.33 (m, 1 H), 2.36−2.45 (m, 1 H), 2.91 (dt, *J* = 2.8, 8.1 Hz, 1 H), 3.00 (dt, *J* = 6.9, 6.9 Hz, 1 H), 3.68 (dd, *J* = 4.8, 7.3 Hz, 1 H), 3.70−3.76 (m, 1 H), 5.15−5.45 (br. s, 1 H, missing after deuteration) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ '= 15.2 (t), 22.2 (t), 26.5 (t), 26.8 (t), 27.9 (t), 46.8 (t), 54.5 (d), 57.2 (d), 63.7 (d), 73.6 (d), 80.5 (d) ppm. MS: *m*/*z* = 194 [M$^+$]. IR: $\tilde{\nu}$ = 3250 cm^{-1}. $C_{11}H_{18}N_2O$ (194.28): calcd. C, 68.01, H 9.34, N 14.42; found C 68.13, H 9.14, N 14.39.

Treatment of 13 with $LiAlH_4$: A solution of $LiAlH_4$ in THF (1 M, 1.4 mL, 1.4 mmol) was added to a solution of **13** (42 mg, 0.22 mmol) in THF (10 mL). After stirring at room temperature for 24 h, the mixture was treated with H_2O (0.7 mL), 10% aqueous NaOH (0.7 mL) and then H_2O (5 mL). THF was removed under reduced pressure and the residue was extracted with CH_2Cl_2; the organic layer was dried with Na_2SO_4, and the solvents were evaporated under reduced pressure to give **10** (31 mg, 72%).

Hydrogenation of 7a with $Pd(OH)_2$/C in MeOH: By the procedure described for the cycloadduct **5a**, compound **7a** (100 mg, 0.34 mmol) gave (+)-(4a*S*,8*R*,8a*S*,9*R*)-9-amino-5,6,7,8,8a,9-hexahydro-4a*H*-pyrrolo[1,2-*a*]indol-8-ol (**9**) (13 mg, 20%). $[\alpha]_D$ = +70.0 (*c* = 0.18, $CHCl_3$).

Hydrogenation of 8a with $Pd(OH)_2$/C in MeOH: By the procedure described for the cycloadduct **5a**, compound **8a** (100 mg, 0.34 mmol) gave (−)-(4a*R*,8*S*,8a*R*,9*S*)-9-amino-5,6,7,8,8a,9-hexahydro-4a*H*-pyrrolo[1,2-*a*]indol-8-ol (**9**) (14 mg, 22%). $[\alpha]_D$ = −69.2 (*c* = 0.20, $CHCl_3$).

Hydrogenation of 7a with $Pd(OH)_2$/C and HCl (1 equiv.) in MeOH: Upon hydrogenation as described for the cycloadduct **5a**, compound **7a** (100 mg, 0.34 mmol) gave (+)-(4a*S*,8*R*,8a*S*,9a*R*)-

Table 1. Crystal data and structure refinement of compounds **5a** and **7a**

	5a	**7a**
Crystal data		
Empirical formula	$C_{18}H_{20}N_2O$	$C_{19}H_{22}N_2O$
Formula mass	280.36	294.39
Crystal dimensions [mm]	0.3 × 0.4 × 0.5	0.4 × 0.4 × 0.45
Crystal system	monoclinic	orthorhombic
Space group	*P*21/*c*	*P*212121
a [Å]	10.062(2)	5.808(0)
b [Å]	15.361(2)	14.038(2)
c [Å]	9.689(2)	19.565(3)
α [°]	90	90
β [°]	99.29(0)	90
γ [°]	90	90
Volume [Å^3]	1477.9(5)	1595.2(3)
Z	4	4
Density (calcd.) [g cm^{-3}]	1.260	1.226
μ [mm^{-1}]	0.617	0.595
F(000)	600	632
Data collection		
Diffractometer	Siemens P4	Siemens P4
Radiation, wavelength [Å]	Cu-K_α, 1.54179	Cu-K_α, 1.54179
No. refl. for cell determination	30	52
θ range for cell determination [°]	7−35	9−37
θ range of data collection [°]	5.8−57.3	3.8−67.8
Completeness to 2θ	94.6%	94.3%
Scan type	θ/2θ	θ/2θ
hkl limits	−10/10; −16/16; −10/10	−5/1; −16/1; −1/23
No. of total refl. collected	4208	2179
No. of ind. refl./*R*(int)	1980/0.0408	2009/0.097
No. of observed refl. [$I > 2\sigma(I)$]	1851	1891
Refinement		
Refinement method	full-matrix, least squares on F^2	full-matrix, least squares on F^2
Data/restraints/parameters	1980/0/191	2009/0/217
Goodness of fit on F^2	1.128	1.104
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0492, wR_2 = 0.1250	R_1 = 0.0629, wR_2 = 0.1662
R indices (all data)	R_1 = 0.0541, wR_2 = 0.1296	R_1 = 0.0652, wR_2 = 0.1708
Extinction coefficient	0.027(2)	0.0062(16)
Largest diff. peaks and holes [e·Å^{-3}]	0.15 and −0.14	0.20 and −0.36

2,3,4a,5,6,7,8,8a,9,9a-decahydro-1*H*-pyrrolo[1,2-*a*]indol-8-ol (**11**) (25 mg, 41%) and (+)-(4a*S*,8*R*,8a*S*,9*R*,9a*R*)-9-amino-2,3,4a,5,6,7,8,8a,9,9a-decahydro-1*H*-pyrrolo[1,2-*a*]indol-8-ol (**10**) (6 mg, 9%). (+)-**10**: $[\alpha]_D = +24.1$ ($c = 0.22$, $CHCl_3$). (+)-**11**: $[\alpha]_D = +56.2$ ($c = 0.24$, $CHCl_3$).

Hydrogenation of 8a with Pd(OH)$_2$/C and HCl (1 equiv.) in MeOH: Upon hydrogenation as described for the cycloadduct **5a**, compound **8a** (100 mg, 0.34 mmol) gave (−)-(4a*R*,8*S*,8a*R*,9a*S*)-2,3,4a,5,6,7,8,8a,9,9a-decahydro-1*H*-pyrrolo[1,2-*a*]indol-8-ol (**11**) (38 mg, 61%) and (−)-(4a*R*,8*S*,8a*R*,9*S*,9a*S*)-9-amino-2,3,4a,5,6,7,8,8a,9,9a-decahydro-1*H*-pyrrolo[1,2-*a*]indol-8-ol (**10**) (6 mg, 9%). (−)-**10**: $[\alpha]_D = -23.2$ ($c = 0.36$, $CHCl_3$). (−)-**11**: $[\alpha]_D = -57.5$ ($c = 0.20$, $CHCl_3$).

Hydrogenation of 7b with Pd(OH)$_2$/C and HCl (1 equiv.) in MeOH: A mixture of Pd/C (10%, 60 mg) and **7b** (100 mg, 0.24 mmol) in a solution of HCl in MeOH (0.02 N, 15 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 50% NaOH solution and extracted with CH_2Cl_2. After evaporation of the solvent, the crude product was chromatographed on silica gel with $CHCl_3$/MeOH (9:1) as eluent to give (−)-(1*R*,4a*S*,11a*S*)-2,3,4,4a,11,11a-hexahydro-1*H*-indolo[1,2-*a*]indol-1-ol (**14**) (25 mg, 38%). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04 (m, 1 H), 1.25−1.67 (3 H, overlapping, 2 H after deuteration), 1.75 (m, 1 H), 1.88 (m, 1 H), 2.18 (m, 1 H), 2.90−3.05 (2 H, overlapping), 3.30 (m, 1 H), 4.11 (ddd, 1 H, J = 5.6, 5.8, 11.1 Hz), 4.45 (ddd, 1 H, J = 6.3, 6.3, 10.7 Hz), 6.19 (s, 1 H), 7.00−7.11 (2 H, overlapping), 7.23 (d, J = 7.8 Hz, 1 H), 7.54 (d, J = 7.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ '= 21.0 (t), 23.8 (t), 28.6 (t), 30.5 (t), 40.5 (d), 56.2 (d), 70.1 (d), 94.0 (d), 109.6 (d), 119.5 (d), 120.6 (d), 120.9 (d), 132.5 (s), 133.2 (s), 142.6 (s) ppm. MS: m/z = 227 [M^+]. IR: $\tilde{\nu}$ = 3350 cm^{-1}. $[\alpha]_D = -196.0$ ($c = 0.10$, $CHCl_3$). $C_{15}H_{17}NO$ (227.31): calcd. C 79.26, H 7.54, N 6.16; found C 79.31, H 7.39, N 6.00.

Hydrogenation of 8b with Pd(OH)$_2$/C and HCl (1 equiv.) in MeOH: Upon hydrogenation as described for the cycloadduct **7b**, compound **8b** (100, 0.29 mmol) gave (+)-(1*S*,4a*R*,11a*R*)-2,3,4,4a,11,11a-hexahydro-1*H*-indolo[1,2-*a*]indol-1-ol (**14**) (23 mg, 36%). $[\alpha]_D = +196.2$ ($c = 0.13$, $CHCl_3$).

X-ray Crystallographic Study: Details of crystal data, as well as of data collection and refinement, are reported in Table 1. Both structures were solved by direct methods using the SIR97 program[8] and refined by full-matrix least-squares procedures with SHELXL-97,[9] with anisotropic temperature factors for all non-H atoms. H atoms were added at idealised positions and refined isotropically in a riding model. Molecular graphics was performed with SHELXTL/PC[10] and material for publications was prepared with SHELXL-97.[9] CCDC-170221 and -170222 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

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[6] When recorded at room temperature, the ^{1}H and ^{13}C NMR spectra of **5a, 7a, 7b, 8a**, and **8b** had little diagnostic value because of their broad signals. When measured at −40 °C, the spectra showed two sets of signals, plausibly corresponding to invertomers at the pyramidal nitrogen of the isoxazolidine ring.

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