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Regiochemical aspects of intramolecular cycloadditions of nitrones derived from *N*-(2-alkenyl)-2-pyrrolecarbaldehydes. Competitive entries to pyrrolizidine and indolizidine derivatives

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Abstract—Intramolecular cycloadditions of unsaturated nitrones derived from a series of *N*-(2-alkenyl)-2-pyrrolecarbaldehydes (**2**) have been systematically studied. A pronounced substituent effect has been observed as far as the competitive formation of fused- and bridged-ring regioisomers are concerned. Further elaboration of the two kinds of cycloadducts has given pyrrolizidine and indolizidine derivatives, respectively. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Intramolecular cycloaddition of a nitrone functionality to the ethylenic bond[1,2] constitutes a flexible and powerful methodology which has resulted in the synthesis of an impressive array of bioactive compounds, both natural and unnatural, such as alkaloids,[2,3] terpenes,[4] sugar analogues,[5] modified nucleosides,[6] and β-lactam antibiotics.[7] Novel and fruitful applications of this methodology, where new stereogenic centres are often formed under relative and/or absolute stereocontrol, are continually appearing in the chemical literature.[8]

Our previous contribution to this area was concerned with the synthesis of enantiopure 3-hydroxymethylchromanes of potential interest as α-adrenergic blocking agents.[9] Later, we turned our attention towards pyrrolizidines and indolizidines structurally related to alkaloids endowed with cytostatic activities.[10] Having in mind these targets, nitrones derived from *N*-(2-alkenyl)substituted 2-pyrrolecarbaldehydes were conceived as appropriate intermediates. The first, albeit promising, results were limited to the simple *N*-allyl-2-pyrrolecarbaldehyde (**2e**).[11] In the present paper, with the aim of better defining the scope and limitations of our synthetic approach, we describe a systematic study involving a number of related substrates.

2. Results and discussion

2.1. Intramolecular nitrone cycloadditions

In light of the above purpose, we synthesized the substituted 2-pyrrolecarbaldehydes **2a**–**d** and treated them with benzylhydroxylamine in order to generate the unsaturated nitrones **3a**–**d** (Scheme 1). Heat treatment of the latter gave two kinds of intramolecular cycloadducts, namely the fused-ring compounds **4** and the bridged-ring compounds **5**. In both instances, however, the relative configuration of the newly-created stereogenic centres was unique as a consequence of the following concomitant features: (i) the concerted, i.e. stereoconservative, mechanism of the cycloaddition and (ii) the forced *cis*-junction of the two formed rings. The latter constriction would not have been operative in intermolecular nitrone cycloadditions, which usually exhibit lower degrees of diastereoselection unless stringent steric demands or attractive secondary interactions are involved.[2a,12]

As far as the regiochemical outcome of the cycloaddition is concerned, the isolation yields reported in Scheme 1 reveal a marked substituent effect, which is possibly steric more than electronic in origin. Molecular models show that the formation of the bridged-ring product requires the disposition of the pendent dipolarophile to be towards the inside of the molecule (Fig. 1).

Therefore, encumbering substituents at the dipolarophilic site should work against such a disposition. In line with this view, the bridged-ring product is formed to the greatest

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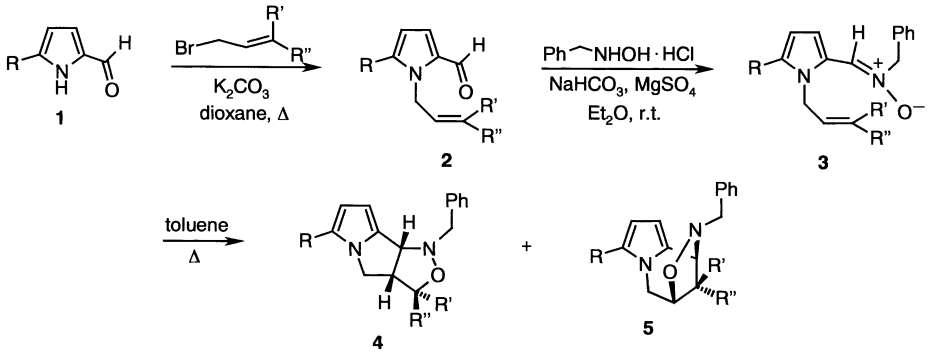


Entry	R	R'	R"	4 (%)[a]	5 (%)[a]
a	H	H	Ph	80	15
b	H	H	C_3H_7	58	10
c	H	CH_3	CH_3	83	—
d	C_4H_9	H	H	25	44
e	H	H	H	34[b]	57[b]

Scheme 1. Intramolecular cycloaddition reactions of nitrones **3**. [a]Isolation yield of pure product after column chromatography. [b]From Ref. [11].

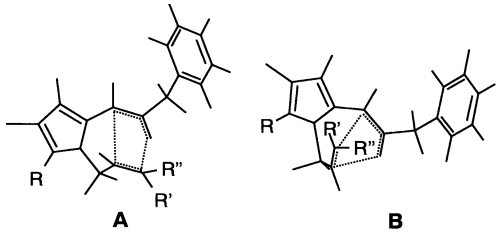
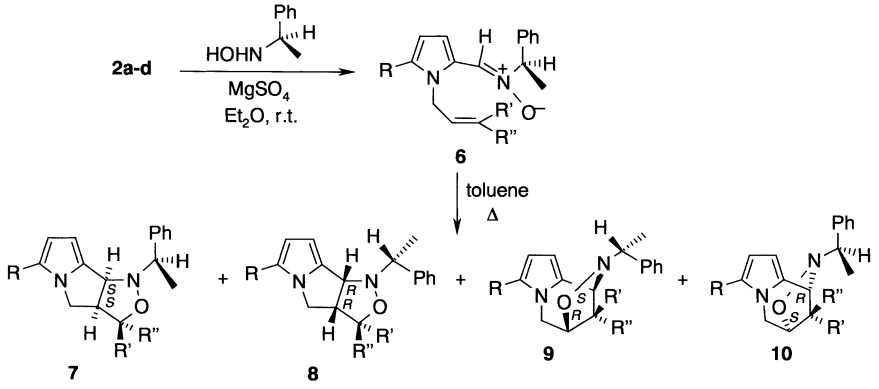


Figure 1. Regioisomeric approaches for the intramolecular cycloaddition of nitrones **3** to give fused-ring (**A**) and bridged-ring (**B**) adducts.

extent in the case of the most simple substrate **3e**, while it is not formed at all in the case of **3c** having two methyl groups on the dipolarophilic double bond. Recent papers[13] have pointed out that a complex interplay of factors intervenes to dictate the regiochemistry of intramolecular nitrone cycloadditions, such that prediction of product outcomes may well be a complex matter.

A similar regiochemical trend was observed when we reacted the same aldehydes **2a–d** with (*R*)-α-methylbenzylhydroxylamine in order to synthesize optically active compounds. Actually, the intramolecular cycloaddition of the first-formed nitrones **6a–d** resulted in two diastereoisomeric pairs of regioisomers (Scheme 2). The regiochemical proportions roughly reflect those observed for the corresponding nitrones **3a–d**, although the formation of bridged-ring structures was generally depressed owing to the increase of the steric hindrance exerted by the *N*-pendant of the dipole.

Absolute configurations were assigned to the cycloadducts on the basis of the NMR evidence, corroborated by the X-ray diffractometric analysis of **7d** (Fig. 2). The latter demonstrated that, due to the spatial location of the phenyl ring, the pyrrolic hydrogen in the 3-position (δ_H=5.37 ppm) suffers from a shielding effect. On the other hand, a conformational analysis by molecular models indicated that such



Entry	R	R'	R"	7 (%)	8 (%)	9 (%)	10 (%)
a	H	H	Ph	36	21	12	4
b	H	H	C_3H_7	36	22	3	2
c	H	CH_3	CH_3	56	8	—	—
d	C_4H_9	H	H	15	20	17	6

Scheme 2. Intramolecular cycloaddition reactions of nitrones **6**.

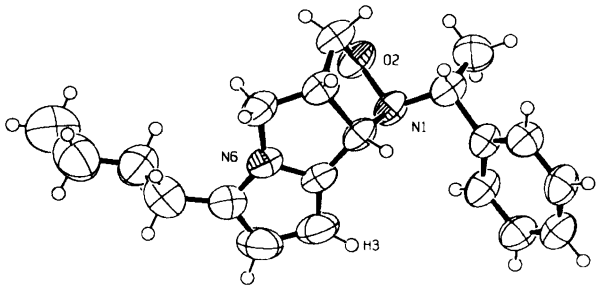


Figure 2. Structure of **7d** determined by X-ray analysis. Thermal ellipsoids at 50% probability level.

Table 1. Observed chemical shifts of the pyrrolic 3-hydrogens

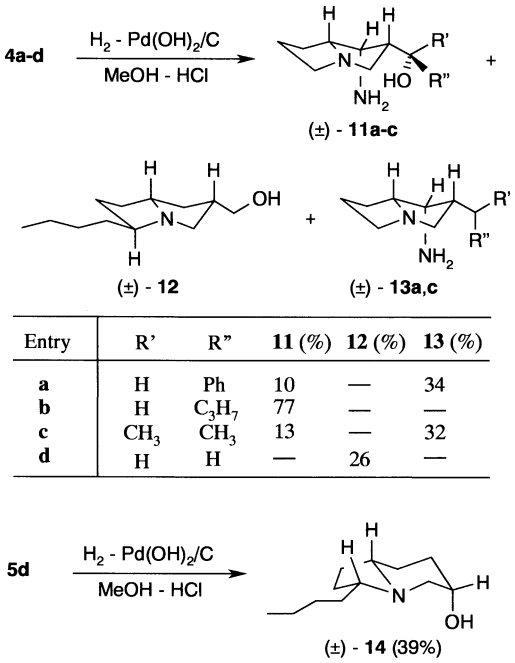
Entry	7	8	9	10
A	4.70	5.81	6.13	5.60
B	4.78	5.83	6.08	5.53
C	5.28	5.85	–	–
D	5.37	5.83	5.91	5.54

an effect is possible only for one isomer of each diastereoisomeric pair. Consequently, the observed differences between the chemical shifts of the pyrrolic 3-hydrogens became fully diagnostic (Table 1).

2.2. Elaboration of the cycloadducts

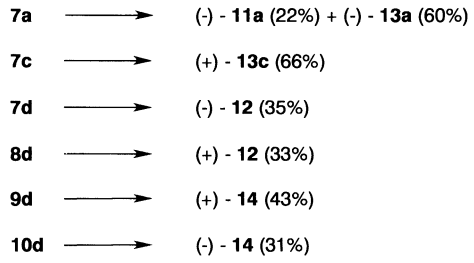
The second part of our study was focused on the elaboration of the above described cycloadducts, particularly with the idea of bringing to light the latent functionalities of the isoxazolidine ring. Furthermore, we perceived that saturation of the pyrrole nucleus would give pyrrolizidine or indolizidine derivatives more strictly related to natural alkaloids. In order to gain these targets, catalytic hydrogenation was chosen as the most appropriate procedure. Experimental results concerning racemic cycloadducts are outlined in Scheme 3.

The requisite saturation of the pyrrole nucleus took place only when operating in the presence of HCl. These strongly protic conditions, on the other hand, induced concurrent pathways: (i) the complete loss of the pseudobenzylic amino group in the case of **4d** and **5d**, which afforded **12** and **14**, respectively; (ii) the partial removal of the alcoholic function, if tertiary or benzylic, so determining the formation of **13a**,**c**. Stereochemical assignments to the products, which contain newly created stereocentre(s), were based upon the following NMR considerations: (i) the electron pair of the bridge-head nitrogen exerts a pronounced deshielding effect on the α-hydrogens only if they are *cis* disposed; (ii) the axial disposition of the hydroxyl group in **14** is proven by the NMR signal of the adjacent hydrogen which does not exhibit any large, i.e. diaxial, coupling constant. The total diastereoselection observed in the saturation of the pyrrole nucleus must be stressed as a noteworthy feature. Literature data[14] indicate that *cis*-2,5-disubstituted pyrrolidines are preferred products in the catalytic hydrogenation of pyrroles. Therefore, the formation of **12** is somewhat surprising and may be tentatively accounted for



Entry	R'	R"	11 (%)	12 (%)	13 (%)
a	H	Ph	10	—	34
b	H	C_3H_7	77	—	—
c	CH_3	CH_3	13	—	32
d	H	H	—	26	—

Scheme 3. Hydrogenation reactions of cycloadducts **4a**–**d** and **5d**.



Scheme 4. Hydrogenation reactions of optically active cycloadducts: MeOH–HCl with $Pd(OH)_2/C$ as catalyst.

by steric demands due to the *cis*-fusion of the pyrrolizidine skeleton.

The hydrogenolytic treatment of optically active cycloadducts, summarized in Scheme 4, allowed the isolation of pyrrolizidine aminoalcohol **11a**, alcohol **12**, amines **13a**,**c** and indolizidine alcohol **14** in enantiopure form. The enantiomeric purity was verified in the case of (+)-**14** and (−)-**14** by recording the ^{1}H NMR spectra at 300 MHz in the presence of (*R*)-(+)-*O*-acetylmandelic acid.

3. Conclusion

In light of the results here reported, one can conclude that intramolecular cycloadditions of nitrones available from *N*-(2-alkenyl)-2-pyrrolecarbaldehydes constitute an efficient and stereoselective route to pyrrolizidine derivatives. The same sequence may serve to achieve indolizidine derivatives with dependence on the regiochemical outcome of the intramolecular cycloaddition, namely provided that no structural factors, steric in nature, work against the formation of bridged-ring cycloadducts.

4. Experimental

4.1. General

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

4.1.1. 5-Butyl-2-pyrrolecarbaldehyde (1). Phosphorus oxychloride (8.9 g, 58 mmol) in dry toluene (8 mL) was added, at 5–10°C, to a stirred solution of dimethylformamide (5 mL) in dry toluene (6 mL). After 30 min, 2-butylpyrrole[15] (6.4 g, 52 mmol) in dimethylformamide (6 mL) was added at 5–10°C. The solution was stirred for 1 h at 20°C, then poured in ice–water (60 mL). Until a basic solution was obtained, 10% aqueous NaOH was added and the product was extracted into chloroform. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give 5.49 g (70%) of **1**.[16]

4.1.2. 1-Cinnamyl-2-pyrrolecarbaldehyde (2a). Cinnamyl bromide (3.2 g, 16 mmol), triethylbenzyl ammonium bromide (170 mg, 0.5 mmol) and 50% aqueous NaOH (6 mL) were added to a solution of 2-pyrrolecarbaldehyde (1.0 g, 10 mmol) in benzene (32 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 1.98 g (57%) of **2a**. Oil. ^1H NMR (300 MHz, $CDCl_3$): δ=5.15 (2H, d, J=5.9 Hz), 6.29 (1H, dd, J=2.5, 4.0 Hz), 6.36 (1H, dt, J=5.9, 15.8 Hz), 6.49 (1H, d, J=15.8 Hz), 6.99 (1H, dd, J=1.7, 4.0 Hz), 7.05 (1H, br s), 7.22–7.39 (5H, overlapping), 9.60 (1H, s). MS: m/z 211 (M^+). IR: ν 1673 cm^{-1}.

4.1.3. 1-(2-Hexenyl)-2-pyrrolecarbaldehyde (2b). A solution of 2-pyrrolecarbaldehyde (0.95 g, 10 mmol) in dioxane (20 mL) was treated with K_2CO_3 (4.8 g, 35 mmol) and 2-hexenyl bromide (4.9 g, 30 mmol). The suspension was refluxed for 24 h, then diluted with toluene (60 mL) and filtered through celite. The solvent was removed under reduced pressure to give 1.63 g (92%) of **2b**. Oil. ^1H NMR (300 MHz, $CDCl_3$): δ=0.86 (3H, t, J=7.4 Hz), 1.37 (2H, tq, J=7.4, 7.4 Hz), 1.94–2.04 (2H, m), 4.89 (2H, d, J=4.2 Hz), 5.54–5.67 (2H, m), 6.22 (1H, dd, J=3.9, 2.6 Hz), 6.92 (1H, dd, J=3.9, 1.5 Hz), 6.96 (1H, br s), 9.53 (1H, s). MS: m/z 177 (M^+). IR: ν 1666 cm^{-1}.

4.1.4. 1-Prenyl-2-pyrrolecarbaldehyde (2c). The compound was prepared as described in the literature.[17]

4.1.5. 1-Allyl-5-butyl-2-pyrrolecarbaldehyde (2d). According to the preceding procedure, 5-butyl-2-pyrrolcarbaldehyde and allyl bromide gave **2d** (62%). Oil. ^1H NMR (300 MHz, $CDCl_3$): δ=0.94 (3H, t, J=7.4 Hz), 1.40 (2H, tq, J=7.4, 7.4 Hz), 1.56–1.70 (2H, m), 2.54 (2H, t, J=7.5 Hz), 4.74 (1H, dd, J=1.2, 17.1 Hz), 4.91–5.04 (2H, m), 5.08 (1H, dd, J=1.2, 10.3 Hz), 5.93 (1H, tdd, J=4.6, 10.3, 17.1 Hz), 6.06 (1H, d, J=3.9 Hz), 6.88 (1H, d, J=3.9 Hz), 9.40 (1H, s). MS: m/z 191 (M^+). IR: ν 1672 cm^{-1}.

4.2. General procedure for the synthesis of nitrones 3a–d

A suspension of *N*-benzylhydroxylamine hydrochloride (7.0 mmol), $MgSO_4$ (85 mmol) and $NaHCO_3$ (12 mmol) in dry diethyl ether (100 mL) was stirred for 1 h, then a solution of **2** (5.6 mmol) in diethyl ether was added. The mixture was stirred for the time given below, filtered and evaporated. The crude oil so obtained was crystallized with diisopropyl ether (entries b and c) or chromatographed on a silica gel column (entries a and d) to give **3a–d**.

4.2.1. Nitrone 3a. 48 h. Eluent: ethyl acetate. Yield: 60%. Mp 141–143°C. ^1H NMR (300 MHz, $CDCl_3$): δ=4.60–4.63 (2H, overlapping), 4.97 (2H, s), 6.13–6.15 (2H, overlapping), 6.29 (1H, dd, J=2.9, 3.7 Hz), 6.82 (1H, dd, J=1.6, 2.9 Hz), 7.26–7.46 (11H, overlapping), 7.85 (1H, dd, J=1.6, 3.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ=50.0 (t), 74.6 (t), 109.3 (d), 117.8 (d), 124.1 (d), 125.0 (s), 125.2 (d), 125.9 (d), 126.1 (d), 128.1 (d), 128.5 (d), 128.8 (d), 129.0 (d), 129.2 (d), 132.5 (d), 136.0 (s), 138.8 (s). MS: m/z 316 (M^+). $C_{21}H_{20}N_2O$ (316.4): calcd C 79.72, H 6.37, N 8.85; found C 79.57, H 6.49, N 8.66.

4.2.2. Nitrone 3b. 72 h. Yield: 84%. Mp 111–113°C (from diisopropyl ether). ^1H NMR (300 MHz, $CDCl_3$): δ=0.86 (3H, t, J=7.4 Hz), 1.33 (2H, tq, J=7.4, 7.4 Hz), 1.93 (2H, dt, J=7.4, 7.4 Hz), 4.37 (2H, d, J=5.2 Hz), 4.99 (2H, s), 5.28–5.41 (2H, m), 6.24 (1H, dd, J=3.0, 3.5 Hz), 6.77 (1H, dd, J=1.7, 3.0 Hz), 7.30–7.43 (6H, overlapping), 7.81 (1H, dd, J=1.7, 3.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.6 (q), 22.0 (t), 34.0 (t), 49.3 (t), 69.5 (t), 109.0 (d), 116.6 (d), 124.0 (s), 124.5 (d), 125.2 (d), 125.4 (d), 128.8 (d), 128.9 (d), 129.2 (d), 132.3 (s), 133.9 (d). MS: m/z 282 (M^+). $C_{18}H_{22}N_2O$ (282.4): calcd C 76.56, H 7.85, N 9.92; found C 76.39, H 7.99, N 10.05.

4.2.3. Nitrone 3c. 168 h. Yield: 59%. Mp 123–124°C (from diisopropyl ether). ^1H NMR (300 MHz, $CDCl_3$): δ=1.59 (3H, s), 1.69 (3H, s), 4.40 (2H, d, J=6.6 Hz), 5.00 (2H s), 5.14 (1H, br t, J=6.6 Hz), 6.22 (1H, dd, J=3.0, 3.7 Hz), 6.76 (1H, dd, J=1.7, 3.0 Hz), 7.22 (1H, s), 7.36–7.43 (5H, overlapping), 7.82 (1H, dd, J=1.7, 3.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.3 (q), 25.9 (q), 46.0 (t), 70.0 (t), 109.3 (d), 117.0 (d), 120.5 (d), 124.4 (s),124.9 (d), 125.8 (d), 128.8 (d), 129.2 (d), 129.8 (d), 133.9 (s), 136.4 (s). MS: m/z 268 (M^+). $C_{17}H_{20}N_2O$ (268.4): calcd C 76.09, H 7.51, N 10.44; found C 76.18, H 7.33, N 10.38.

4.2.4. Nitrone 3d. 96 h. Eluent: hexane/ethyl acetate 1:1. Yield: 41%. Mp 75–78°C (from diisopropyl ether). ^1H NMR (300 MHz, $CDCl_3$): δ=0.91 (3H, t, J=7.3 Hz), 1.36 (2H, tq, J=7.3, 7.5 Hz), 1.53–1.61 (2H, m), 2.49 (2H, t, J=7.5 Hz), 4.33–4.39 (2H, m), 4.63 (1H, d, J=17.1 Hz), 4.97 (2H, s), 5.06 (1H, d, J=10.5 Hz), 5.75 (1H, ddt, J=4.5, 10.5, 17.1 Hz), 6.05 (1H, d, J=3.9 Hz), 7.14 (1H, s), 7.33–7.42 (5H, overlapping), 7.80 (1H, d, J=3.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.8 (q), 22.4 (t), 26.2 (t),

30.6 (t), 45.5 (t), 69.3 (t), 107.8 (d), 115.9 (d), 116.5 (t), 123.7 (s), 124.7 (d), 128.6 (d), 128.8 (d), 129.3 (d), 133.3 (d), 133.6 (s), 138.4 (s). MS: *m/z* 296 (M^+). $C_{19}H_{24}N_2O$ (296.4): calcd C 76.99, H 8.16, N 9.45; found C 77.04, H 8.02, N 9.61.

4.3. General procedure for the cycloaddition reaction of nitrones 3a–d

A solution of **3** (4.8 mmol) in toluene (90 mL) was refluxed for 24 h. After evaporation of the solvent, the residue was chromatographed on a silica gel column.

Entry a—Elution with toluene/ethyl acetate 15:1 gave **5a** (15%) and **4a** (80%).

4.3.1. (3*R,3a*R**,8b*R**)-1-Benzyl-3-phenyl-1,3a,4,8b-tetrahydro-3*H*-isoxazolo[3,4-*a*]pyrrolizine (4a).** Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.78–3.86 (1H, m), 4.06–4.17 (3H, overlapping), 4.32 (1H, d, *J*=12.9 Hz), 4.50 (1H, br s), 4.94 (1H, d, *J*=7.2 Hz), 5.35 (1H, br s), 6.18 (1H, br s), 6.55 (1H, br s), 7.26–7.46 (10H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$): δ=49.5 (t), 59.9 (d), 61.2 (t) 69.6 (d), 86.0 (d), 102.1 (d), 104.1 (s), 114.1 (d), 115.0 (d), 127.3 (d), 128.2 (d), 128.7 (d), 128.9 (d), 129.2 (d), 130.4 (d), 137.2 (s), 139.3 (s). MS: *m/z* 316 (M^+). $C_{21}H_{20}N_2O$ (316.4): calcd C 79.72, H 6.37, N 8.85; found C 79.75, H 6.24, N 8.98.

4.3.2. (1*R,4*R**,10*R**)-2-Benzyl-10-phenyl-1,2,4,5-tetrahydro-1,4-methanopyrrolo[2,1-*d*][1,2,5]oxadiazepine (5a).** Mp 102–104°C (from diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.62, 3.66 (2H, AB, *J*=14.0 Hz), 3.70 (1H, br s), 4.19, 4.27 (2H, AB, *J*=12.3 Hz), 4.27 (1H, br s), 4.77 (1H, br s), 5.98 (1H, dd, *J*=1.5, 3.3 Hz), 6.23 (1H, dd, *J*=3.0, 3.3 Hz), 6.72 (1H, dd, *J*=1.5, 3.0 Hz), 7.20–7.40 (8H, overlapping), 7.55–7.58 (2H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$): δ=54.0 (t), 54.2 (d), 58.4 (t), 61.5 (d), 77.1 (d), 106.6 (d), 108.3 (d), 120.0 (d), 126.8 (d), 127.0 (d), 128.1 (d), 128.2 (d), 128.3 (d), 128.4 (d), 129.6 (s), 137.8 (s), 139.7 (s). MS: *m/z* 316 (M^+). $C_{21}H_{20}N_2O$ (316.4): calcd C 79.72, H 6.37, N 8.85; found C 79.61, H 6.44, N 9.02.

Entry b—Elution with light petroleum/dichloromethane/diethyl ether 10:4:1 gave **5b** (10%) and **4b** (58%).

4.3.3. (3*R,3a*S**,8b*S**)-1-Benzyl-3-propyl-1,3a,4,8b-tetrahydro-3*H*-isoxazolo[3,4-*a*]pyrrolizine (4b).** Mp 79–81°C (from hexane/benzene). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.96 (3H, t, *J*=7.2 Hz), 1.32–1.79 (4H, overlapping), 3.36–3.48 (1H, m), 3.92–4.09 (3H, overlapping), 4.03, 4.18 (2H, AB, *J*=12.9 Hz), 4.29 (1H, br d, *J*=7.2 Hz), 5.31 (1H, br s), 6.14 (1H, dd, *J*=3.0, 3.1 Hz), 6.51 (1H, dd, *J*=1.5, 3.1 Hz), 7.28–7.42 (5H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.6 (q), 19.8 (t), 35.9 (t), 49.6 (t), 57.8 (d), 68.6 (t), 69.3 (d), 84.0 (d), 101.7 (d), 113.7 (d), 114.6 (d), 127.8 (d), 128.7 (d), 130.0 (d), 133.9 (s), 137.31 (s). MS: *m/z* 282 (M^+). $C_{18}H_{22}N_2O$ (282.4): calcd C 76.56, H 7.85, N 9.92; found C 76.71, H 7.70, N 10.07.

4.3.4. (1*R,4*S**,10*R**)-2-Benzyl-10-propyl-1,2,4,5-tetrahydro-1,4-methanopyrrolo[2,1-*d*][1,2,5]oxadiazepine (5b).** Mp 76–78°C (from diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.96 (3H, t, *J*=7.3 Hz), 1.43 (2H, tq, *J*=7.3, 7.5 Hz), 1.66–1.89 (2H, m), 2.44 (1H, dd, *J*=7.3, 7.4 Hz), 3.57 (2H, s), 4.02 (1H, dd, *J*=1.7, 12.3 Hz), 4.05 (1H, br s), 4.16 (1H, dd, *J*=2.1, 12.3 Hz), 4.43 (1H, br s), 5.91 (1H, dd, *J*=1.5, 3.3 Hz), 6.14 (1H, dd, *J*=3.1, 3.3 Hz), 6.65 (1H, dd, *J*=1.5, 3.1 Hz), 7.19–7.37 (5H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.9 (q), 20.6 (t), 32.1 (t), 49.2 (d), 53.8 (t), 58.5 (t), 59.5 (d), 76.6 (d), 106.4 (d), 108.1 (d), 119.7 (d), 127.1 (d), 128.6 (d), 128.9 (d), 129.9 (s), 137.98 (s). MS: *m/z* 282 (M^+). $C_{18}H_{22}N_2O$ (282.4): calcd C 76.56, H 7.85, N 9.92; found C 76.65, H 7.66, N 9.86.

Entry c—Elution with light petroleum/diethyl ether 3:1 gave **4c** (83%).

4.3.5. (3a*R,8b*R**)-1-Benzyl-3,3-dimethyl-1,3a,4,8b-tetrahydro-3*H*-isoxazolo[3,4-*a*]pyrrolizine (4c).** Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.29 (3H, s), 1.41 (3H, s), 3.51 (1H, dt, *J*=3.9, 8.2 Hz), 3.93 (1H, dd, *J*=8.2, 11.2 Hz), 4.09 (1H, dd, *J*=3.9, 11.2 Hz), 4.11, 4.17 (2H, AB, *J*=13.2 Hz), 4.51 (1H, br s), 5.57 (1H, br s), 6.19 (1H, t, *J*=3.0 Hz), 6.56 (1H, br d, *J*=3.0 Hz), 7.23–7.34 (3H, overlapping), 7.36–7.44 (2H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.8 (q), 28.2 (q), 46.3 (t), 59.8 (d), 67.9 (d), 80.11 (t), 94.5 (s), 101.4 (d), 112.8 (d), 114.0 (d), 126.9 (d), 128.3 (d), 130.2 (d), 137.5 (s), 154.3 (s). MS: *m/z* 268 (M^+). $C_{17}H_{20}N_2O$ (268.4): calcd C 76.09, H 7.51, N 10.44; found C 75.89, H 7.38, N 10.61.*Entry d*—Elution with hexane/dichloromethane/diethyl ether 5:4:1 gave **4d** (25%) and **5d** (44%).

4.3.6. (3a*R,8b*R**)-1-Benzyl-6-butyl-1,3a,4,8b-tetrahydro-3*H*-isoxazolo[3,4-*a*]pyrrolizine (4d).** Mp 65–67°C (from diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.91 (3H, t, *J*=7.3 Hz), 1.36 (2H, qt, *J*=7.3, 7.5 Hz), 1.49–1.61 (2H, m), 2.47 (2H, t, *J*=7.5 Hz), 3.82 (1H, dd, *J*=3.3, 3.6 Hz), 3.84–3.96 (2H, overlapping), 4.01, 4.12 (2H, AB, *J*=13.4 Hz), 4.04 (1H, dd, *J*=2.0, 7.9 Hz), 4.24 (1H, br s), 4.43 (1H, br s), 5.66 (1H, br s), 5.90 (1H, d, *J*=3.0 Hz), 7.22–7.36 (3H, overlapping), 7.38–7.43 (2H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.9 (q), 22.5 (t), 26.3 (t), 31.1 (t), 49.1 (t), 51.0 (d), 68.6 (d), 72.4 (t), 100.9 (d), 109.7 (d), 110.3 (s), 127.4 (d), 128.1 (d), 129.1 (d), 133.7 (s), 137.4 (s). MS: *m/z* 296 (M^+). $C_{19}H_{24}N_2O$ (296.4): calcd C 76.99, H 8.16, N 9.45; found C 77.08, H 8.27, N 9.64.

4.3.7. (1*R,4*S**)-2-Benzyl-7-butyl-1,2,4,5-tetrahydro-1,4-methanopyrrolo[2,1-*d*][1,2,5]oxadiazepine (5d).** Mp 61–63 °C (from diisopropyl ether). *Major conformer*: ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.97 (3H, t, *J*=7.3 Hz), 1.43 (2H, qt, *J*=7.3, 7.5 Hz), 1.56 (2H, tt, *J*=7.3, 7.5 Hz), 2.26 (1H, d, *J*=10.9 Hz), 2.52 (2H, dt, *J*=7.3, 7.3 Hz), 2.80 (1H, ddd, *J*=4.6, 6.7, 10.9 Hz), 3.51, 3.62 (2H, AB, *J*=13.4 Hz), 3.79 (1H, d, *J*=12.2 Hz), 3.99 (1H, d, *J*=12.2 Hz), 4.26 (1H, d, *J*=4.4 Hz), 4.77 (1H, br d, *J*=4.5 Hz), 5.87–5.96 (2H, overlapping), 7.20–7.42 (5H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.9 (q), 22.6 (t), 25.9 (t), 30.7 (t), 35.9 (t), 51.3 (t), 56.7 (d), 59.1 (t), 72.5 (d), 104.3 (d), 106.3 (d), 115.3 (s), 127.1 (d), 128.3 (d), 129.2 (d), 135.5 (s), 137.7 (s). *Minor conformer*: ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.97 (3H, t, *J*=7.3 Hz), 1.43 (2H, qt, *J*=7.3, 7.5 Hz), 1.56 (2H, tt, *J*=7.3, 7.5 Hz), 2.16–2.23 (1H, m), 2.37–2.50 (2H, m), 2.62–2.73 (1H, m), 3.52–4.18 (5H,

overlapping), 4.91–5.00 (1H, m), 5.76–5.85 (2H, overlapping), 7.20–7.42 (5H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.9 (q), 22.6 (t), 25.9 (t), 31.6 (t), 35.9 (t), 50.5 (t), 56.7 (d), 63.0 (t), 73.6 (d), 104.3 (d), 106.3 (d), 115.3 (s), 127.1 (d), 128.3 (d), 129.1 (d), 135.6 (s), 137.7 (s). MS: *m/z* 296 (M^+). $C_{19}H_{24}N_2O$ (296.4): calcd C 76.99, H 8.16, N 9.45; found C 76.83, H 8.09, N 9.43.

4.4. General procedure for the synthesis of nitrones 6a–c

A suspension of (*R*)-*N*-(α-methylbenzyl)hydroxylamine (5.5 mmol), **2a–d** (4.8 mmol) and $MgSO_4$ (70 mmol) in dry diethyl ether (100 mL) was stirred for the time given below, filtered and evaporated. The crude oil so obtained was treated with diisopropyl ether (entry c) or chromatographed on a silica gel column (entries a, b and d) to give **6a–d**.

4.4.1. Nitrone 6a. 48 h. Eluent: ethyl acetate. Yield: 49%. Mp 100–102°C (from diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.86 (3H, d, *J*=6.9 Hz), 4.65 (2H, d, *J*=4.0 Hz), 5.08 (1H, q, *J*=6.9 Hz), 6.17 (1H, dt, *J*=4.0, 16.2 Hz), 6.21 (1H, d, *J*=16.2 Hz), 6.30 (1H,dd, *J*=2.8, 3.8 Hz), 6.83 (1H, dd, *J*=1.7, 2.8 Hz), 7.24–7.42 (11H, overlapping), 7.86 (1H, dd, *J*=1.7, 3.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ=19.4 (q), 49.8 (t), 74.0 (d), 109.7 (d), 117.0 (d), 123.6 (d), 124.8 (s), 125.2 (d), 126.0 (d), 126.9 (d), 127.8 (d), 128.5 (d), 128.9 (d), 129.1 (d), 129.2 (d), 132.5 (d), 136.3 (s), 139.1 (s). MS: *m/z* 330 (M^+). $[\alpha]_D^{22}$=+38.0 (*c*=0.10, $CHCl_3$). $C_{22}H_{22}N_2O$ (330.4): calcd C 79.97, H 6.71, N 8.48; found C 79.91, H 6.56, N 8.33.

4.4.2. Nitrone 6b. 120 h. Eluent: hexane/ethyl acetate 1:1. Yield: 45%. Mp 93–95°C (from diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (3H, t, *J*=7.2 Hz), 1.32 (2H, qt, *J*=7.2, 7.4 Hz), 1.87 (3H, d, *J*=6.9 Hz), 1.83–1.97 (2H, m), 4.39 (2H, d, *J*=5.1 Hz), 5.09 (1H, q, *J*=6.9 Hz), 5.27–5.46 (2H, overlapping), 6.23 (1H, dd, *J*=2.8, 3.7 Hz), 6.75 (1H, dd, *J*=1.6, 2.8 Hz), 7.30–7.48 (5H, overlapping), 7.00–7.64 (1H, m), 7.80 (1H, dd, *J*=1.6, 3.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.6 (q), 19.1 (q), 22.0 (t), 34.0 (t), 49.3 (t), 73.4 (d), 109.0 (d), 116.7 (d), 123.9 (d), 123.9 (s), 125.3 (d), 125.6 (d), 127.3 (d), 128.4 (d), 128.5 (d), 133.9 (d), 138.8 (d). MS: *m/z* 296 (M^+). $[\alpha]_D^{22}$=+13.9 (*c*=0.14, $CHCl_3$). $C_{19}H_{24}N_2O$ (296.4): calcd C 76.99, H 8.16, N 9.45; found C 77.12, H 8.01, N 9.64.

4.4.3. Nitrone 6c. 144 h. Yield: 36%. Mp 89–90°C (from diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.62 (3H, s), 1.66 (3H, s), 1.88 (3H, d, *J*=6.9 Hz), 4.42 (2H, d, *J*=6.6 Hz), 5.09 (1H, q, *J*=6.9 Hz), 5.15 (1H, br t, *J*=6.6 Hz), 6.21 (1H, dd, *J*=2.1, 3.9 Hz), 6.76 (1H, dd, *J*=1.6, 2.1 Hz), 7.30–7.40 (4H, overlapping), 7.44–7.48 (2H, overlapping), 7.81 (1H, dd, *J*=1.6, 3.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.4 (q), 19.6 (q), 25.9 (q), 45.9 (t), 74.0 (d), 109.2 (d), 116.8 (d), 120.6 (d), 123.6 (d), 124.5 (s), 125.6 (d), 112.7 (d), 128.9 (d), 129.1 (d), 136.4 (s), 139.4 (s). MS: *m/z* 282 (M^+). $[\alpha]_D^{22}$=+32.0 (*c*=0.10, $CHCl_3$). $C_{18}H_{22}N_2O$ (282.4): calcd C 76.56, H 7.85, N 9.92; found C 76.75, H 7.68, N 10.08.

4.5. General procedure for the cycloaddition reaction of nitrones 6a–c

A solution of **6a–c** (1.9 mmol) in toluene (40 mL) was refluxed for 24 h. After evaporation of the solvent, the residue was chromatographed on a silica gel column.

Entry a—Elution with toluene gave **10a** (4%), **9a** (12%) and a third fraction, which was chromatographed with light petroleum/diethyl ether 3:1 as eluent to give **8a** (21%) and **7a** (36%).

4.5.1. (α*R*,3*S*,3a*S*,8b*S*)-3-Phenyl-1-(α-phenylethyl)-1,3a,4,8b-tetrahydro-3*H*-isoxazolo[3,4-*a*]pyrrolizine (7a). Mp 98–99°C (from hexane/benzene). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.63 (3H, d, *J*=6.5 Hz), 3.60–3.74 (1H, m), 3.93–4.12 (3H, overlapping), 4.62–4.78 (2H, overlapping), 4.86 (1H, d, *J*=7.9 Hz), 6.05 (1H, br s), 6.46 (1H, br s), 7.34–7.49 (10H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.4 (q), 48.1 (t), 59.3 (d), 69.1 (d), 84.7 (d), 85.4 (d), 102.5 (d), 113.2 (s), 114.2 (d), 114.8 (d), 127.4 (d), 128.7 (d), 128.9 (d), 129.3 (d), 129.4 (d), 129.7 (d), 138.8 (s), 142.8 (s). MS: *m/z* 330 (M^+). $[\alpha]_D^{22}$=+46.0 (*c*=0.10, $CHCl_3$). $C_{22}H_{22}N_2O$ (330.4): calcd C 79.97, H 6.71, N 8.48; found C 79.99, H 6.66, N 8.64.

4.5.2. (α*R*,3*R*,3a*R*,8b*R*)-3-Phenyl-1-(α-phenylethyl)-1,3a,4,8b-tetrahydro-3*H*-isoxazolo[3,4-*a*]pyrrolizine (8a). Mp 57–58°C (from hexane/benzene). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.57 (3H, d, *J*=6.8 Hz), 3.49–3.63 (1H, m), 3.99 (1H, dd, *J*=8.0, 10.8 Hz), 4.08 (1H, dd, *J*=3.8, 10.8 Hz), 4.14 (1H, q, *J*=6.8 Hz), 4.43 (1H, d, *J*=8.8 Hz), 4.79 (1H, d, *J*=7.2 Hz), 5.81 (1H, d, *J*=3.5 Hz), 6.21 (1H, dd, *J*=3.0, 3.5 Hz), 6.53 (1H, d, *J*=3.0 Hz), 7.19–7.38 (8H, overlapping), 7.42 (2H, d, *J*=8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ=21.9 (q), 49.1 (t), 59.9 (d), 65.0 (d), 66.3 (d), 84.2 (s), 85.3 (d), 102.4 (d), 113.9 (d), 115.0 (d), 127.0 (d), 127.6 (d), 128.6 (d), 128.7 (d), 128.9 (d), 129.0 (d), 134.9 (s), 142.6 (s). MS: *m/z* 330 (M^+). $[\alpha]_D^{22}$=+31.8 (*c*=0.10, $CHCl_3$). $C_{22}H_{22}N_2O$ (330.4): calcd C 79.97, H 6.71, N 8.48; found C 79.89, H 6.89, N 8.30.

4.5.3. (α*R*,1*S*,4*S*,10*S*)-10-Phenyl-2-(α-phenylethyl)-1,2,4,5-tetrahydro-1,4-methanopyrrolo[2,1-*d*][1,2,5]oxadiazepine (9a). Mp 150–152°C (from hexane/benzene). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.22 (3H, d, *J*=6.5 Hz), 3.31 (1H, q, *J*=6.5 Hz), 3.69 (1H, s), 4.11 (1H, dd, *J*=1.7, 12.3 Hz), 4.23 (1H, dd, *J*=2.2, 12.3 Hz), 4.46 (1H, s), 4.69 (1H, br s), 6.13 (1H, br s), 6.26 (1H, t, *J*=3.2 Hz), 6.72 (1H, br s), 7.13–7.43 (8H, overlapping), 7.57–7.60 (2H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.8 (q), 54.6 (t), 54.7 (d), 60.6 (d), 63.5 (d), 77.1 (d), 106.9 (d), 108.8 (d), 120.5 (d), 127.2 (d), 127.4 (d), 127.6 (d), 128.8 (d), 128.9 (d), 129.3 (d), 130.0 (s), 140.5 (s), 145.5 (s). MS: *m/z* 330 (M^+). $[\alpha]_D^{22}$=+80.0 (*c*=0.10, $CHCl_3$). $C_{22}H_{22}N_2O$ (330.4): calcd C 79.97, H 6.71, N 8.48; found C 79.94, H 6.80, N 8.59.

4.5.4. (α*R*,1*R*,4*R*,10*R*)-10-Phenyl-2-(α-phenylethyl)-1,2,4,5-tetrahydro-1,4-methanopyrrolo[2,1-*d*][1,2,5]oxadiazepine (10a). Mp 52–53°C (from diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.42 (3H, d, *J*=6.3 Hz), 3.36 (1H, q, *J*=6.3 Hz), 3.56 (1H, s), 4.06 (1H, s), 4.16 (1H, dd, *J*=1.8, 12.2 Hz), 4.30 (1H, dd, *J*=2.2, 12.2 Hz), 4.77 (1H,

dd, J=1.8, 2.2 Hz), 5.60 (1H, dd, J=1.6, 3.5 Hz), 6.16 (1H, dd, J=3.0, 3.5 Hz), 6.70 (1H, dd, J=1.6, 3.0 Hz), 7.14–7.41 (8H, overlapping), 7.57–7.61 (2H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$): δ=23.6 (q), 54.2 (d), 54.3 (t), 59.7 (d), 63.3 (d), 77.3 (d), 107.1 (d), 108.0 (d), 119.6 (d), 126.9 (d), 127.6 (d), 127.8 (d), 128.1 (d), 128.2 (d), 128.3 (d), 129.9 (s), 140.0 (s), 143.5 (s). MS: m/z 330 (M^+). $[\alpha]_D^{22}$=+111.0 (c=0.16, $CHCl_3$). $C_{22}H_{22}N_2O$ (330.4): calcd C 79.97, H 6.71, N 8.48; found C 80.11, H 6.65, N 8.37.

Entry b—Elution with light petroleum/diethyl ether 8:1 gave **8b** (22%), **7b** (36%) and a third fraction which was re-chromatographed with light petroleum/dichloromethane/diethyl ether 20:4:1 as eluant to give **10b** (2%) and **9b** (3%).

4.5.5. (α*R*,3*R*,3a*S*,8b*S*)-1-(α-Phenylethyl)-3-propyl-1,3a,4,8b-tetrahydro-3*H*-isoxazolo[3,4-*a*]pyrrolizine (7b). Mp 73–75°C (from diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$, 55°C): δ=0.98 (3H, t, J=7.3 Hz), 1.47 (2H, qt, J=7.3, 7.5 Hz), 1.58 (3H, d, J=6.4 Hz), 1.59–1.82 (2H, m), 3.32 (1H, dddd, J=3.2, 8.1, 8.3, 8.5 Hz), 3.84–3.99 (4H, overlapping), 4.45 (1H, d, J=8.5 Hz), 4.78 (1H, br s), 6.04 (1H, dd, J=3.0, 3.1 Hz), 6.42 (1H, dd, J=1.5, 3.0 Hz), 7.27–7.44 (5H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.2 (q), 19.6 (t), 21.6 (q), 35.7 (t), 48.1 (t), 56.7 (d), 66.0 (d), 69.5 (d), 83.0 (d), 101.6 (d), 113.2 (d), 113.8 (d), 127.8 (d), 128.5 (d), 128.8 (d), 128.9 (s), 192.0 (s). MS: m/z 296 (M^+). $[\alpha]_D^{22}$=+10.4 (c=0.07, $CHCl_3$). $C_{19}H_{24}N_2O$ (296.4): calcd C 76.99, H 8.16, N 9.45; found C 76.98, H 8.27, N 9.29.

4.5.6. (α*R*,3*S*,3a*R*,8b*R*)-1-(α-Phenylethyl)-3-propyl-1,3a,4,8b-tetrahydro-3*H*-isoxazolo[3,4-*a*]pyrrolizine (8b). Mp 71–73°C (from diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.91 (3H, t, J=7.2 Hz), 1.25–1.52 (3H, overlapping), 1.54 (3H, d, J=6.9 Hz), 1.62–1.70 (1H, m), 3.25 (1H, dddd, J=3.9, 8.0, 8.2, 8.7 Hz), 3.85 (1H, q, J=6.9 Hz), 3.93 (1H, dd, J=3.9, 10.7 Hz), 4.02 (1H, dd, J=8.2, 10.7 Hz), 4.04 (1H, ddd, J=7.4, 7.9, 8.0 Hz), 4.32 (1H, br d, J=8.7 Hz), 5.83 (1H, d, J=3.0 Hz), 6.24 (1H, dd, J=3.0, 3.0 Hz), 6.54 (1H, br d, J=3.0 Hz), 7.21–7.33 (3H, overlapping), 7.40–7.43 (2H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.1 (q), 19.3 (t), 21.6 (q), 35.3 (t), 48.9 (t), 57.1 (d), 64.7 (d), 65.9 (d), 83.0 (d), 102.0 (d), 113.3 (d), 114.3 (d), 127.1 (d), 127.9 (d), 128.1 (d), 135.1 (s), 142.8 (s). MS: m/z 296 (M^+). $[\alpha]_D^{22}$=+48.0 (c=0.4, $CHCl_3$). $C_{19}H_{24}N_2O$ (296.4): calcd C 76.99, H 8.16, N 9.45; found C 77.07, H 8.01, N 9.53.

4.5.7. (α*R*,1*S*,4*R*,10*S*)-2-(α-Phenylethyl)-10-propyl-1,2,4,5-tetrahydro-1,4-methanopyrrolo[2,1-*d*][1,2,5]oxadiazepine (9b). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.00 (3H, t, J=7.3 Hz), 1.28 (3H, d, J=6.5 Hz), 1.44–1.50 (2H, m), 1.70–1.94 (2H, overlapping), 2.42 (1H, t, J=7.2 Hz), 3.19 (1H, br q, J=6.5 Hz), 3.95 (1H, dd, J=2.4, 12.3 Hz), 4.09 (1H, dd, J=1.8, 12.3 Hz), 4.30 (1H, s), 4.34 (1H, br s), 6.08 (1H, br s), 6.22 (1H, br t, J=2.1 Hz), 6.65 (1H, br s), 7.17–7.34 (5H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0 (q), 20.6 (t), 22.2 (q), 32.2 (t), 49.0 (d), 53.8 (t), 57.9 (d), 62.8 (d), 76.1 (d), 106.0 (d), 107.9 (d), 119.7 (d), 126.6 (d), 126.9 (d), 128.2 (d), 130.0 (s), 145.0 (s). MS: m/z 296 (M^+). $[\alpha]_D^{22}$=+108.0 (c=0.23, $CHCl_3$). $C_{19}H_{24}N_2O$ (296.4): calcd C 76.99, H 8.16, N 9.45; found C 76.83, H 8.36, N 9.28.

4.5.8. (α*R*,1*R*,4*S*,10*R*)-2-(α-Phenylethyl)-10-propyl-1,2,4,5-tetrahydro-1,4-methanopyrrolo[2,1-*d*][1,2,5]oxadiazepine (10b). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.95 (3H, t, J=7.3 Hz), 1.37 (3H, d, J=6.3 Hz), 1.28–1.46 (2H, overlapping), 1.74–1.85 (2H, m), 2.31 (1H, t, J=7.3 Hz), 3.26 (1H, t, J=6.3 Hz), 3.84 (1H, s), 3.99 (1H, dd, J=1.7, 12.2 Hz), 4.16 (1H, dd, J=2.2, 12.2 Hz), 4.46 (1H, s), 5.53 (1H, dd, J=1.4, 3.4 Hz), 6.11 (1H, dd, J=3.4, 3.4 Hz), 6.62 (1H, dd, J=1.4, 3.4 Hz), 7.24–7.33 (5H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0 (q), 20.6 (t), 23.5 (q), 32.1 (t), 48.9 (d), 53.8 (t), 57.9 (d), 63.1 (d), 76.7 (d), 106.9 (d), 107.8 (d), 119.3 (d), 127.0 (d), 127.4 (s), 127.9 (d), 128.1 (d), 136.9 (s). MS: m/z 296 (M^+). $[\alpha]_D^{22}$=−15.0 (c=0.08, $CHCl_3$). $C_{19}H_{24}N_2O$ (296.4): calcd C 76.99, H 8.16, N 9.45; found C 77.13, H 7.98, N 9.51.

Entry c—Elution with light petroleum/diethyl ether 7:1 gave **8c** (8%) and **7c** (56%).

4.5.9. (α*R*,3a*S*,8b*S*)-3,3-Dimethyl-1-(α-phenylethyl)-1,3a,4,8b-tetrahydro-3*H*-isoxazolo[3,4-*a*]pyrrolizine (7c). Mp 58–59°C (from diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.16 (3H, s), 1.42 (3H, s), 1.53 (3H, d, J=6.5 Hz), 3.41 (1H, dt, J=2.6, 7.7 Hz), 3.88 (1H, dd, J=7.7, 11.2 Hz), 3.99–4.08 (2H, overlapping), 4.70 (1H, br s), 5.28 (1H, br s), 6.13 (1H, br s), 6.50 (1H, br s), 7.23–7.35 (3H, overlapping), 7.40–7.44 (2H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.7 (q), 22.9 (q), 29.2 (q), 46.9 (d), 59.7 (d), 65.9 (d), 66.2 (d), 80.9 (s), 102.2 (d),108.3 (s), 113.5 (d), 114.3 (d), 127.7 (d), 128.4 (d), 128.8 (d), 138.0 (s). MS: m/z 282 (M^+). $[\alpha]_D^{22}$=+42.4 (c=0.10, $CHCl_3$). $C_{18}H_{22}N_2O$ (282.4): calcd C 76.56, H 7.85, N 9.92; found C 76.64, H 7.99, N 10.02.

4.5.10. (α*R*,3a*R*,8b*R*)-3,3-Dimethyl-1-(α-phenylethyl)-1,3a,4,8b-tetrahydro-3*H*-isoxazolo[3,4-*a*]pyrrolizine (8c). Mp 55–56°C (from diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.24 (3H, s), 1.35 (3H, s), 1.48 (3H, d, J=6.6 Hz), 3.38 (1H, dt, J=2.9, 8.2 Hz), 3.86 (1H, dd, J=8.2, 11.2 Hz), 4.00–4.11 (2H, overlapping), 4.49 (1H, d, J=8.2 Hz), 5.85 (1H, d, J=3.1 Hz), 6.23 (1H, t, J=3.1 Hz), 6.56 (1H, d, J=3.1 Hz), 7.20–7.33 (3H, overlapping), 7.43 –7.46 (2H, overlapping). MS: m/z 282 (M^+). $C_{18}H_{22}N_2O$ (282.4): calcd C 76.56, H 7.85, N 9.92; found C 76.49, H 7.78, N 9.77.

4.6. Cycloaddition reaction between 2d and (*R*)-*N*-(α-phenylethyl)hydroxylamine via nitrone 6d

A suspension of (*R*)-*N*-(α-phenylethyl)hydroxylamine (10.1 mmol), **2d** (5.7 mmol) and $MgSO_4$ (86.4 mmol) in dry toluene (110 mL) was refluxed under stirring for 48 h. After filtration and evaporation of the solvent, the residue was chromatographed on a silica gel column with hexane/ethyl acetate 3:1 as eluent to give **8d** (20%), **7d** (15%), **9d** (17%) and **10d** (6%).

4.6.1. (α*R*,3a*S*,8b*S*)-1-(α-Phenylethyl)-6-butyl-1,3a,4,8b-tetrahydro-3*H*-isoxazolo[3,4-*a*]pyrrolizine (7d). Mp 116–117°C (from diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$, 55°C): δ=0.84 (3H, t, J=7.3 Hz), 1.29 (2H, qt, J=7.3, 7.5 Hz), 1.44 (3H, d, J=6.4 Hz), 1.42–1.49 (2H, m), 2.38 (2H, t, J=7.3 Hz), 3.68–3.77 (3H, overlapping),

3.84–3.94 (2H, overlapping), 4.14 (1H, dd, J=7.5, 9.3 Hz), 4.51 (1H, br d, J=7.1 Hz), 5.37 (1H, br d, J=3.0 Hz), 5.78 (1H, d, J=3.0 Hz), 7.16–7.29 (3H, overlapping), 7.33–7.37 (2H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ=13.8 (q), 22.1 (q), 22.4 (t), 26.2 (t), 31.2 (t), 49.3 (t), 50.4 (d), 63.5 (d), 67.0 (d), 72.1 (t), 109.8 (d), 109.8 (d), 110.0 (s), 127.5 (d), 127.9 (d), 128.1 (s), 128.5 (d), 143.6 (s). MS: m/z 310 (M^+). $[\alpha]_D^{22}$=−6.9 (c=0.10, $CHCl_3$). $C_{20}H_{26}N_2O$ (310.4): calcd C 77.38, H 8.44, N 9.02; found C 77.29, H 8.42, N 9.09.

4.6.2. (α*R*,3a*R*,8b*R*)-1-(α-Phenylethyl)-6-butyl-1,3a,4,8b-tetrahydro-3*H*-isoxazolo[3,4-*a*]pyrrolizine (8d). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.91 (3H, t, J=7.2 Hz), 1.36 (2H, qt, J=7.5, 7.6 Hz), 1.51 (3H, d, J=6.6 Hz), 1.48–1.60 (2H, overlapping), 2.47 (2H, t, J=7.5 Hz), 3.68–3.84 (3H, overlapping), 3.92–4.04 (2H, overlapping), 4.14 (1H, dd, J=7.3, 8.1 Hz), 4.48 (1H, br d, J=7.5 Hz), 5.83 (1H, br s), 5.93 (1H, d, J=3.4 Hz), 7.21–7.43 (5H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ=12.4 (q), 13.9 (q), 22.5 (t), 26.3 (t), 31.2 (t), 48.6 (t), 51.2 (d), 62.0 (d), 66.7 (d), 72.2 (t), 101.7 (d), 109.9 (d), 127.1 (d), 128.3 (d), 129.2 (d), 136.6 (s), 143.1 (s), 155.9 (s). MS: m/z 310 (M^+). $[\alpha]_D^{22}$=+54.0 (c=0.05, $CHCl_3$). $C_{20}H_{26}N_2O$ (310.4): calcd C 77.38, H 8.44, N 9.02; found C 77.51, H 8.30, N 8.88.

4.6.3. (α*R*,1*S*,4*R*)-2-(α-Phenylethyl)-7-butyl-1,2,4,5-tetrahydro-1,4-methanopyrrolo[2,1-*d*][1,2,5]oxadiazepine (9d). Compound present as a 3:2 mixture of two conformers. Oil. *Major conformer*: ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.94 (3H, br s), 1.31 (3H, br d, J=5.7 Hz), 1.42–1.65 (4H, overlapping), 2.25 (1H, br d, J=10.9 Hz), 2.43–2.61 (2H, m), 2.80 (1H, br s), 3.18 (1H, br d, J=5.5 Hz), 3.73 (1H, br s), 3.90 (1H, br s), 4.50 (1H, br s), 4.66 (1H, br s), 5.91 (1H, br s), 6.05 (1H, br s), 7.20–7.35 (5H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$): δ=4.1 (q), 21.6 (q), 22.5 (t), 25.9 (t), 31.4 (t), 35.8 (t), 51.3 (t), 55.1 (d), 63.3 (d), 72.0 (d), 104.1 (d), 104.3 (d), 127.0 (d), 127.3 (d), 128.2 (d), 129.5 (s), 133.4 (s), 144.6 (s). *Minor conformer*: ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.94 (3H, br s), 1.41 (3H, br d, J=7.3 Hz), 1.42–1.65 (4H, overlapping), 2.08 (1H, br d, J=10.6 Hz), 2.43–2.61 (2H, m), 3.72–3.76 (2H, overlapping), 3.88–4.02 (2H, overlapping), 4.13 (1H, br s), 4.96 (1H, br s), 5.61 (1H, br s), 5.75 (1H, br s), 7.20–7.35 (5H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0 (q), 22.5 (q), 22.6 (t), 25.9 (t), 31.5 (t), 35.8 (t), 50.4 (t), 55.5 (d), 66.7 (d), 73.8 (d), 102.3 (d), 105.9 (d), 127.0 (d), 127.5 (d), 128.7 (d), 129.4 (s), 133.3 (s), 143.7 (s). MS: m/z 310 (M^+). $[\alpha]_D^{22}$=−25.0 (c=0.12, $CHCl_3$). $C_{20}H_{26}N_2O$ (310.4): calcd C 77.38, H 8.44, N 9.02; found C 77.26, H 8.59, N 8.84.

4.6.4. (α*R*,1*R*,4*S*)-2-(α-Phenylethyl)-7-butyl-1,2,4,5-tetrahydro-1,4-methanopyrrolo[2,1-*d*][1,2,5]oxadiazepine (10d). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.96 (3H, t, J=7.2 Hz), 1.41 (3H, d, J=6.4 Hz), 1.34–1.48 (2H, m), 1.50–1.67 (2H, m), 2.13 (1H, d, J=11.0 Hz), 2.49 (2H, t, J=7.1 Hz), 2.74 (1H, br s), 3.34 (1H, br s), 3.75 (1H, d, J=11.0 Hz), 3.97 (1H, d, J=11.0 Hz), 4.04 (1H, br s), 4.82 (1H, d, J=6.3 Hz), 5.54 (1H, br s), 5.81 (1H, d, J=3.4 Hz), 7.26–7.33 (5H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0 (q), 22.6 (t), 23.1 (q), 25.9 (t), 30.6 (t), 35.8 (t), 51.3 (t), 55.1 (d), 63.4 (d), 72.4 (d), 103.9 (d), 106.8 (d), 127.0 (d), 128.1 (d), 128.3 (d), 128.5 (s), 130.1 (s), 143.4 (s). MS: m/z 310 (M^+). $[\alpha]_D^{22}$=+60.4 (c=0.27, $CHCl_3$). $C_{20}H_{26}N_2O$ (310.4): calcd C 77.38, H 8.44, N 9.02; found C 77.38, H 8.27, N 9.15.

4.7. General procedure for the hydrogenation reaction of cycloadducts

A mixture of 10% $Pd(OH)_2$/C (100 mg, 0.095 mmol) and isoxazolidinic compound (0.31 mmol) in a 0.06N solution of HCl 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 treated with a solution of NaOH in methanol. The solvent was evaporated under reduced pressure and the residue was taken up into dichloromethane. The organic solution was separated and evaporated, and the crude product was chromatographed on silica gel column.

Compound 4a—Elution with chloroform/methanol/32% aqueous ammonia 7:1:1 gave **13a** (34%) and **11a** (10%).

4.7.1. (α*R,1*R**,2*R**,7a*R**)-1-Amino-2,3,5,6,7,7a-hexahydro-α-phenyl-1*H*-2-pyrrolizinemethanol (11a).** Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.24 (3H, br s, missing after deuteriation), 1.68–1.75 (2H, overlapping), 1.85–2.00 (2H, overlapping), 2.44–2.69 (3H, overlapping), 2.82 (1H, dd, J=6.0, 8.4 Hz), 3.02 (1H, ddd, J=4.6, 6.4, 10.4 Hz), 3.40 (1H, dd, J=4.9, 5.0 Hz), 3.62 (1H, dt, J=5.0, 7.3 Hz), 4.78 (1H, d, J=7.2 Hz), 7.21–7.37 (5H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.6 (t), 28.1 (t), 53.2 (d), 53.8 (d), 54.7 (t), 55.6 (t), 69.9 (d), 73.7 (d), 126.8 (d), 127.9 (d), 128.6 (d), 144.3 (s). MS: m/z 232 (M^+). IR: ν 3435 cm^{-1}. $C_{14}H_{20}N_2O$ (232.3): calcd C 72.38, H 8.68, N 12.06; found C 72.26, H 8.81, N 11.89.

4.7.2. (1*R,2*R**,7a*R**)-1-Amino-2-benzyl-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine (13a).** Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.70–2.00 (4H, overlapping), 2.28 (2H, br s, missing after deuteriation), 2.40–2.51 (2H, overlapping), 2.61–2.81 (3H, overlapping), 3.04–3.15 (3H, overlapping), 3.71 (1H, dt, J=5.0, 7.4 Hz), 7.13–7.32 (5H, overlapping). ^{13}C NMR (75 MHz, $CDCl_3$): δ=24.0 (t), 27.4 (t), 32.8 (t), 47.7 (d), 52.1 (d), 54.3 (t), 55.4 (t), 69.7 (d), 126.5 (d), 128.3 (d), 128.7 (d), 154.0 (s). MS: m/z 216 (M^+). IR: ν 3420 cm^{-1}. $C_{14}H_{20}N_2$ (216.3): calcd C 77.73, H 9.32, N 12.95; found C 77.74, H 9.19, N 13.07.

Compound 4b—Evaporation of the solvent gave **11b** (77%).

4.7.3. (α*R,1*S**,2*R**,7a*S**)-1-Amino-2,3,5,6,7,7a-hexahydro-α-propyl-1*H*-2-pyrrolizinemethanol (11b).** Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.82–0.96 (4H, overlapping), 1.23–1.58 (6H, overlapping, 3H after deuteriation), 1.66–1.76 (2H, overlapping), 1.86–1.98 (2H, overlapping), 2.29–2.54 (3H, overlapping), 3.01–3.10 (2H, overlapping), 3.40 (1H, dd, J=5.1, 5.4 Hz), 3.60 (1H, ddd, J=5.4, 7.5, 7.8 Hz), 3.70 (1H, ddd, J=3.3, 7.6, 7.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.1 (q), 18.8 (t), 24.2 (t), 27.8 (t), 39.0 (t), 52.4 (d), 52.9 (d), 54.3 (t), 55.2 (t), 69.4 (d), 69.9 (d). MS: m/z 198 (M^+). IR: ν 2908, 2957, 3367 cm^{-1}.

$C_{11}H_{22}N_2O$ (198.3): calcd C 66.62, H 11.18, N 14.31; found C 66.89, H 11.40, N 14.43.

Compound 4c—Elution with chloroform/methanol/32% aqueous ammonia 7:1:1 gave **11c** (13%) and **13c** (32%).

4.7.4. (1*R,2*R**,7a*R**)-1-Amino-2,3,5,6,7,7a-hexahydro-α,α-dimethyl-1*H*-2-pyrrolizinemethanol (11c).** Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.15 (3H, s), 1.36 (3H, s), 1.59–1.86 (2H, overlapping), 1.90–2.03 (2H, overlapping), 2.21 (1H, ddd, *J*=4.5, 6.7, 12.5 Hz), 2.32 (3H, br s, missing after deuteriation), 2.45 (1H, dt, *J*=7.1, 9.4 Hz), 2.70 (1H, dd, *J*=9.4, 12.5 Hz), 3.12 (1H, ddd, *J*=3.8, 5.8, 9.4 Hz), 3.25 (1H, dd, *J*=6.7, 9.4 Hz), 3.34 (1H, dd, *J*=4.5, 4.5 Hz), 3.65 (1H, dt, *J*=4.5, 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ=28.7 (t), 29.9 (q), 30.1 (t), 30.8 (q), 52.1 (t), 54.3 (d), 55.2 (d), 56.0 (t), 69.7 (d), 70.8 (s). MS: *m*/*z* 184 (M^+). IR: ν 3435 cm^{-1}. $C_{10}H_{20}N_2O$ (184.3): calcd C 65.18, H 10.94, N 15.20; found C 65.31, H 10.95, N 15.07.

4.7.5. (1*R,2*R**,7a*R**)-1-Amino-2,3,5,6,7,7a-hexahydro-2-(1-methylethyl)-1*H*-pyrrolizine (13c).** Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.04–1.28 (7H, overlapping), 1.28–1.49 (1H, m), 1.59–1.70 (1H, m), 1.74–1.95 (3H, overlapping), 2.08 (2H, br s, missing after deuteriation), 2.14–2.34 (2H, overlapping), 2.52 (1H, dt, *J*=6.1, 10.5 Hz), 2.86 (1H, dt, *J*=6.2, 10.4 Hz), 3.07 (1H, dd, *J*=6.3, 6.6 Hz), 3.48 (1H, dt, *J*=6.3, 7.7, 14.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ=29.1 (q), 29.5 (q), 29.9 (d), 30.5 (t), 33.4 (t), 48.5 (d), 52.2 (d), 54.8 (t), 55.8 (t), 65.9(d). MS: *m*/*z* 168 (M^+). IR: ν 3384, 3335 cm^{-1}. $C_{10}H_{20}N_2$ (168.3): calcd C 71.37, H 11.98, N 16.65; found C 71.31, H 12.10, N 16.61.

Compound 4d—Elution with dichloromethane/methanol/32% aqueous ammonia 6:1:1 gave **12** (26%).

4.7.6. (2*R,5*R**,7a*S**)-5-Butyl-2,3,5,6,7,7a-hexahydro-1*H*-2-pyrrolizinemethanol (12).** Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (3H, t, *J*=6.8 Hz), 1.15 (1H, ddd, *J*=9.4, 9.4, 11.7 Hz), 1.21–1.37 (4H, overlapping), 1.38–1.94 (5H, overlapping, 4H after deuteriation), 1.95–2.12 (3H, overlapping), 2.29 (1H, dd, *J*=9.8, 9.9 Hz), 2.53–2.68 (2H, overlapping), 3.29 (1H, dd, *J*=6.7, 9.4 Hz), 3.58–3.63 (1H, m), 3.65 (2H, d, *J*=6.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0 (q), 22.9 (t), 29.6 (t), 31.9 (t), 34.7 (t), 36.0 (t), 36.1 (t), 45.8 (d), 57.9 (t), 65.3 (t), 65.7 (d), 68.3 (d). MS: *m*/*z* 197 (M^+). IR: ν 3391 cm^{-1}. $C_{12}H_{23}NO$ (197.3): calcd C 73.04, H 11.75, N 7.10; found C 72.98, H 11.91, N 7.01.

Compound 5d—Elution with dichloromethane/methanol/light petroleum 7:2:1 gave **14** (39%).

4.7.7. (3*R,6*S**,8a*R**)-3-Butyl-1,2,3,5,6,7,8,8a-octahydroindolizin-6-ol (14).** Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (3H, t, *J*=6.9 Hz), 1.14–1.47 (8H, overlapping), 1.48–1.74 (3H, overlapping), 1.75–1.89 (3H, overlapping), 1.98–2.03 (1H, m), 2.05 (1H, dd, *J*=1.3, 11.2 Hz), 2.17–2.23 (1H, m), 2.96 (1H, br s, missing after deuteriation), 3.16 (1H, ddd, *J*=2.3, 2.5, 11.3 Hz), 3.88 (1H, br quintet, *J*=2.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0 (q), 23.0 (t), 26.1 (t), 28.0 (t), 28.1 (t), 29.7 (t), 31.9 (t), 32.8 (t), 56.9 (t), 64.3 (d), 64.9 (d), 65.1 (d). MS: *m*/*z* 197 (M^+). IR: ν 3436 cm^{-1}. $C_{12}H_{23}NO$ (197.3): calcd C 73.04, H 11.75, N 7.10; found C 73.08, H 11.64, N 7.00.

Compound 7a—Elution with chloroform/methanol/32% aqueous ammonia 7:1:1 gave (−)-**13a** (60%) and (−)-**11a** (22%).

4.7.8. (α*S*,1*S*,2*S*,7a*S*)-1-Amino-2,3,5,6,7,7a-hexahydro-α-phenyl-1*H*-2-pyrrolizinemethanol (−)-(11a). $[\alpha]_D^{22}$=−17.3 (*c*=0.11, $CHCl_3$).

4.7.9. (1*S*,2*S*,7a*S*)-1-Amino-2-benzyl-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine (−)-(13a). $[\alpha]_D^{22}$=−5.2 (*c*=0.14, $CHCl_3$).

Compound 7c—Elution with chloroform/methanol/32% aqueous ammonia 7:1:1 gave (+)-**13c** (66%).

4.7.10. (1*S*,2*S*,7a*S*)-1-Amino-2,3,5,6,7,7a-hexahydro-2-(1-methylethyl)-1*H*-pyrrolizine (+)-(13c). $[\alpha]_D^{22}$=+8.3 (*c*=0.42, $CHCl_3$).

Compound 7d—Elution with dichloromethane/methanol/32% aqueous ammonia 6:1:1 gave (−)-**12** (35%).

4.7.11. (2*R*,5*R*,7a*S*)-5-Butyl-2,3,5,6,7,7a-hexahydro-1*H*-2-pyrrolizinemethanol (−)-(12). $[\alpha]_D^{22}$=−2.5 (*c*=0.18, $CHCl_3$).

Compound 8d—Elution with dichloromethane/methanol/32% aqueous ammonia 6:1:1 gave (+)-**12** (33%).

4.7.12. (2*S*,5*S*,7a*R*)-5-Butyl-2,3,5,6,7,7a-hexahydro-1*H*-2-pyrrolizinemethanol (+)-(12). $[\alpha]_D^{22}$=+2.1 (*c*=0.18, $CHCl_3$).

Compound 9d—Elution with dichloromethane/methanol/light petroleum 7:2:1 gave (+)-**14** (43%).

4.7.13. (3*S*,6*R*,8a*S*)-3-Butyl-1,2,3,5,6,7,8,8a-octahydroindolizin-6-ol (+)-(14). $[\alpha]_D^{22}$=+48.9 (*c*=0.18, $CHCl_3$).

Compound 10d—Elution with dichloromethane/methanol/light petroleum 7:2:1 gave (−)-**14** (31%).

4.7.14. (3*R*,6*S*,8a*R*)-3-Butyl-1,2,3,5,6,7,8,8a-octahydroindolizin-6-ol (−)-(14). $[\alpha]_D^{22}$=−47.1 (*c*=0.04, $CHCl_3$).

4.8. X-Ray crystallographic study

Single-crystal X-ray diffraction measurement was performed on a Bruker SMART-APEX diffractometer, graphite monochromator, MoKα radiation (λ=0.71073 Å). The crystal data are as follows: $C_{20}H_{26}N_2O$, M_r=310.43, orthorhombic, space group $P2_12_12_1$, *a*=5.2871(7), *b*=14.8271(12), *c*=22.724(2) Å, *V*=1781.4(3) Å^3, *Z*=4, D_c=1.157 g cm^{-3}, μ(MoKα)=0.071 mm^{-1}; 17,714 collected data, R_{ave}=0.0260; final values for 2393[1317 with $I_o > 2\sigma(I_o)$] reflections, $R_w(F2)$=0.1032(0.0980) and *R*=0.0765(0.0408). The absolute configuration was assigned on the knowledge of the stereochemistry at C12. All crystallographic data (excluding structure factors) were deposited

to the Cambridge Crystallographic Data Center as supplementary publication no CCDC-157419. Copies of the data can be obtained free of charge on application to CCDC, 2 Union Road, Cambridge CB2 1EZ, UK, e-mail: deposit@ccdc.cam.ac.uk.

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