DOI: 10.1002/ejoc.200701217

Synthesis of Enantiopure Highly Functionalized Pyrrolizines and Indolizines from Natural α-Amino Acids: An Experimental and Theoretical Investigation

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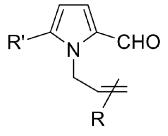
Keywords: Cycloaddition / Nitrones / Regioselectivity / Density functional calculations / Pi interactions

Variously substituted enantiopure 2-benzylamino-1-hydroxymethyl-2,3-dihydro-1*H*-pyrrolizines and 6-benzylamino-5,6,7,8-tetrahydroindolizin-8-ols have been prepared. The reaction sequence starts from L-α-amino acids and involves an intramolecular cycloaddition of pyrrole-based nitrone intermediates. A theoretical investigation at the HCTH/6-311+G(d,p)//HCTH/6-31+G(d) level of theory was performed with the aim of rationalizing the effects of substituents on the regiochemistry of the cycloaddition reaction.

Introduction

Pyrrolizine and indolizine skeletons, partially or totally saturated, are present in a large array of alkaloids and related unnatural compounds. Such compounds exhibit potent biological activities, particularly as glycosidase inhibitors. They consequently have a cytostatic effect that has potential applications in antitumour and antiviral chemotherapy.[1] For the past few years, we have had an interest in the synthesis of such molecules, with intramolecular nitrone cycloaddition reactions[2] being our synthetic methodology of choice. We have succeeded in the preparation of both racemic and enantiopure pyrrolizidines and indolizidines endowed with amino and hydroxy groups by using nitrones derived from 1-allylpyrrole-2-carbaldehydes **1**.[3] We believed that using nitrones derived from 1-(formylmethyl)-2-vinylpyrroles **2** would allow flexibility in the positioning of these important functionalities on the parent skeletons. On the basis of the retrosynthetic analysis of such pyrroles, natural α-amino acids were devised as building blocks for the construction of the pyrrole nucleus, allowing access to chiral non-racemic species.



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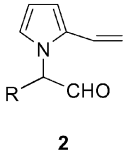

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Although intramolecular nitrone cycloaddition reactions have been known for a long time and their synthetic versatility is well established,[2] the regio- and diastereoselective outcomes of these reactions are a consequence of a subtle interplay of electronic factors and geometric restraints, precluding a sound prediction in most cases. Consequently, we present our experimental work along with the results of an extensive and systematic theoretical investigation.

Results and Discussion

Synthesis

Following the procedure reported in the literature for building the pyrrole nucleus on a primary amino group,[4] we first transformed a series of commercial α-amino acids into chiral non-racemic derivatives (*S*)-**3a**–**e** (Scheme 1). As the heterocyclic ring of the latter required a vinyl residue in the 2-position as a potential dipolarophile, a formyl group was selectively introduced into this position by applying Vilsmeier conditions to (*S*)-**3a**–**e**.[5] For the conversion of the intermediates (*S*)-**4a**–**e** into the desired vinyl derivatives (*S*)-**5a**–**e**, after considering the possible base-promoted racemization under classical Wittig reaction conditions, we chose to carry out the olefination process by using zinc, CH_2I_2 and $TiCl_4$ in the presence of a catalytic amount of $PbCl_2$.[6] In order to introduce the nitrone moiety, the methyl ester group of compounds (*S*)-**5a**–**e** was reduced with DIBAL-H to give the aldehydes (*S*)-**6a**–**e**. However, these aldehydes show a high tendency to degrade, even at a

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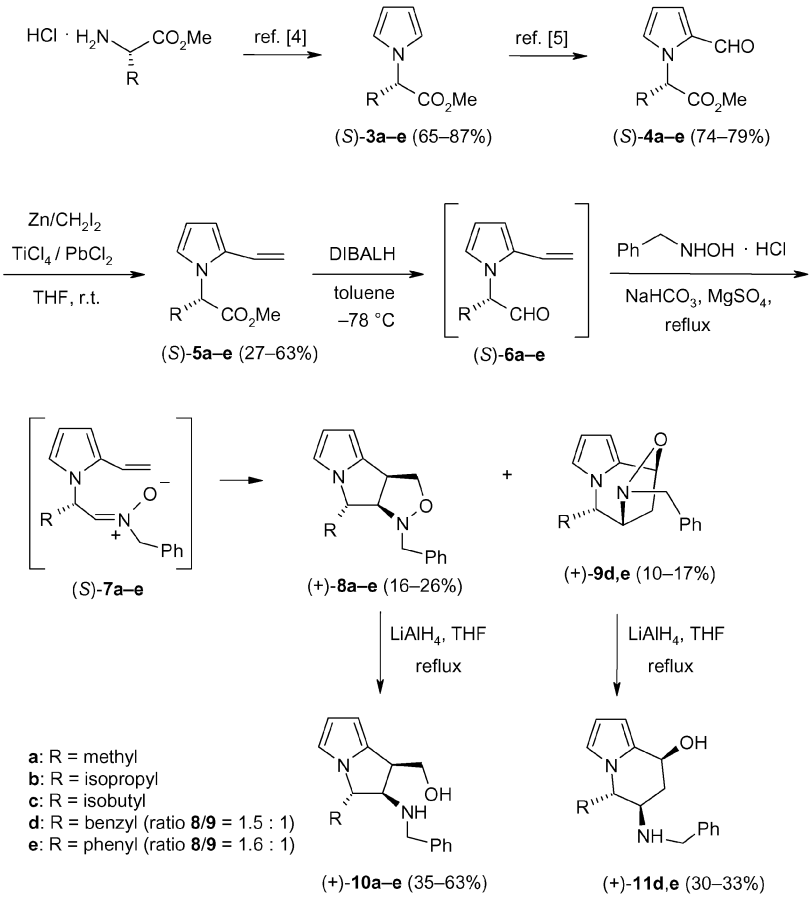


Scheme 1. Cycloaddition process and isoxazolidine ring-opening step.

low temperature, so their use as precursors of nitrones was crucial. Therefore we sought to use a one-pot protocol with no isolation of intermediates (*S*)-**6a**–**e**, namely, by treating the methyl esters (*S*)-**5a**–**e** with DIBAL-H in toluene at –78 °C for 1 h and then adding *N*-benzylhydroxylamine and heating the mixture at reflux for 24 h. Under these conditions, the products resulting from the intramolecular cycloaddition reaction were obtained directly. The isolated yields were moderate, but it must be underlined that they refer to three steps involving the labile aldehydes (*S*)-**6a**–**e**. The final outcome, however, was somewhat different for the different substrates. The fused-ring cycloadducts **8a**–**e** were all formed from the nitrones (*S*)-**7a**–**e**, whereas the bridged-ring compounds **9d**,**e** were observed only with (*S*)-**7d**,**e**.

The two regioisomeric structures were distinguished by ^{1}H and ^{13}C NMR spectroscopy, the different chemical shifts of the endocyclic methylene group being particularly diagnostic. On the other hand, by analogy to previous results concerning the intramolecular cycloaddition of *C*-(1-allyl-2-imidazolyl)nitrones,[7] the stereochemical disposition of the isoxazolidine ring was assumed to be *trans* with respect to the R substituent. The steric hindrance exerted by the R group plausibly justifies such a stereochemical preference.

Next, the isoxazolidine ring of the cycloadducts was manipulated in order to achieve functionalized pyrrolizines and indolizines.[8] The reductive cleavage of the N–O bond was performed by heating at reflux compounds **8a**–**e** and **9d**,**e** in dry THF with $LiAlH_4$ for 24 h. This protocol led to 2,3-dihydropyrrolizines **10a**–**e** and 5,6,7,8-tetrahydroindolizines **11d**,**e**, respectively. The enantiomeric purity of the so-obtained 1,3-amino alcohols was verified to be higher than 98% in one case, namely **10b**, by comparing its ^{1}H NMR spectrum with that of (±)-**10b** (synthesized starting from the racemic valine methyl ester) recorded in the presence of (*R*)-*O*-acetylmandelic acid.

The most striking feature of the above results is the regiochemical outcome of the intramolecular cycloaddition in which the role of the R substituent seems at first glance incongruous. Indeed, it is quite hard to explain the observed regioselectivity by only invoking the different steric hindrances of the substituents because, for example, **7c** and **7d** (R = *i*Bu and Bn, respectively) provide quite a different product distribution even if the encumbrance of the R group is comparable. A contrasting statement could be made for **7a** (R = Me) and **7c** for which a remarkable difference in steric hindrance results in a similar regioselective outcome. At the same time, it must be stressed that the regiochemistry of the cycloaddition determines whether the pyrrolizine or indolizine derivatives are formed as the final products. Such considerations prompted us to undertake the following computational study.

Theoretical Calculations

Although several theoretical investigations on intermolecular nitrone cycloadditions have been reported in the literature,[9] fewer studies concerning intramolecular cycloadditions are available.[7,10] However, none of the reported studies provided us with an unequivocal interpretation of our experimental results, thus the need to perform an "ad hoc" investigation. As the B3LYP/6-31G* methodology, which combines good treatment of the electron correlation with a moderate need for computational power, was extensively adopted in the previously cited articles, it was our first choice for the geometry optimization of reactants **7a**–**e**, products **8a**–**e** and **9a**–**e** and the corresponding transition structures **TS-8a**–**e** and **TS-9a**–**e**. In fact, the energetic results obtained were not consistent with the experimental evidence (see the Supporting Information for the B3LYP/6-31G* energies). Indeed, in every modelled reaction the fused-ring structure **8** was calculated to be the kinetic ($\Delta\Delta E^{\ddagger}_{TS9-TS8}$ = 2.5, 3.6, 2.8, 1.6 and 2.3 kcal/mol for compounds **a**, **b**, **c**, **d** and **e**, respectively) as well as the thermodynamic product with the only exception the methyl-substituted compound ($\Delta\Delta E_{9-8}$ = –1.5, 2.0, 0.8, 0.01 and 0.7 kcal/mol for compounds **a**, **b**, **c**, **d** and **e**, respectively). Therefore we turned our attention to other computational approaches.

Recently it has been reported that diffuse functions are necessary for a proper description of cycloaddition reactions involving nitrones, at least as single-point energy evaluations.[9a] Moreover, in some cases, the inclusion of the solvent effect was important for a reliable estimation of the energetic aspect of these processes.[9b,9e] Indeed, Kuznetsov and Kukushkin showed that the reactivity of cyclic and acyclic nitrones in 1,3-dipolar cycloadditions was well described by single-point CPCM calculations.[9b] For this reason we recomputed the energy of all the stationary points previously located by single-point energy evaluations at the B3LYP/6-311+G(d,p) level of theory, including the solvent contribution by the CPCM model for toluene. Unfortunately, even at this more accurate theoretical level, the computed kinetic and thermodynamic data were overall in discordance with the observed regiochemical outcomes (see the Supporting Information). At the same time, a thorough analysis of the optimized geometries showed the possibility that π–π or CH–π interactions between the R substituent and the nitrone benzyl moiety could play some role in determining the regioselectivity in the transition state. The importance of π–π and CH–π interactions in governing the selectivity of cycloaddition reactions is documented in the literature.[11,12] Furthermore, it is known that the description of dispersive interactions by DFT methods is quite challenging and that in dispersion-bound systems the B3LYP functional often predicts a repulsive instead of an attractive interaction.[13] Although several theoretical methods that accurately describe dispersive interactions are reported in the literature,[14] most of them could not be applied to our investigations owing to either the large demands on computational power or the need for non-standard codes. However, in a recent theoretical study 25 density functionals were compared with CCSD(T) calculations describing dispersion-bound homomolecular dimers,[15] including benzene dimers already described by high-level calculations.[16] Such a comparative investigation evidenced that the PW91 and the HCTH407 functionals were able to predict an attractive interaction in all three possible benzene dimers.[17] Another recent article reported that the hybrid density functional BH&H also provided a good description of the π–π interactions, even if the authors ascribed the good performance to a fortuitous cancellation of errors.[18] For the reasons just mentioned, we decided to model the cycloadditions of **7e** by using the HCTH, PW91 and BH&H functionals. As the best concordance between theoretical calculations and experimental evidence was obtained with the HCTH functional, we undertook a full reoptimization of all the reactants, transition-state structures and products at the HCTH/6-31+G(d) level of theory and single-point energies were recalculated at the HCTH/6-311+G(d,p) level in the gas phase or in solution by the CPCM model for toluene. In fact, the HCTH407 functional provided, at an affordable computational expense, a net improvement in the description of the kinetics and thermodynamics of the reactions considered herein. Indeed, the energetic results summarized in Table 1 (see the Supporting Information for the all energies) fit well with the experimentally observed regiochemistry, which confirms that a good description of the dispersive interactions is essential to the accuracy of our computational model.

Table 1. Activation and reaction free-energy differences [kcal/mol] for the formation of **9** and **8**.[a,b]

Compound (R)	Gas phase		Solvent	
	$\Delta\Delta G^{\ddagger}$	$\Delta\Delta G$	$\Delta\Delta G^{\ddagger}$	$\Delta\Delta G$
a (Me)	0.25	0.96	–0.81	0.20
b (*i*Pr)	1.12	2.98	0.38	3.25
c (*i*Bu)	0.90	4.03	–0.98	1.80
d (Bn)	–2.21	1.76	–3.54	1.92
e (Ph)	–0.38	1.49	–2.13	0.61

[a] Gas-phase and solution Gibbs free energies are calculated as the sum of the single-point HCTH/6-311+G(d,p) energies obtained in vacuo and in solution and the free-energy corrections resulting from the thermochemical analysis. [b] $\Delta\Delta G^{\ddagger}$ and $\Delta\Delta G$ are the total Gibbs free-energy differences between **TS-9** and **TS-8** and the products **9** and **8**, respectively.

Note that the gas-phase energies are slightly more concordant with experiments than those computed in solution, probably because in this latter case an overstabilization of **TS-8a**,**e** arose from the lack of explicit π–π solute–solvent interactions in the implicit solvation model. However, because all the cycloaddition reactions were performed in an apolar solvent such as toluene, gas-phase results can be considered accurate enough for further analyses. The first evidence for the two reaction mechanisms concerns the degree of synchronicity. In a recent article we defined the degree of synchronicity for cycloaddition reactions involving heteroatoms as the difference between the ratios of the forming bond lengths in the TS and the corresponding

bond lengths in the product, that is, $\Delta d_{TS/P} = |(C–O)_{TS}/(C–O)_P – (C–C)_{TS}/(C–C)_P|$. Note that a complete synchronous reaction gives $\Delta d_{TS/P} = 0$.[18]

Analysis of the vibrational motion associated with the unique imaginary frequency computed for **TS-8** and **TS-9** as well as IRC analyses show that both reaction paths are concerted but, as shown in Figure 1 (see Table 1 of the Supporting Information for specific values), the cycloadditions leading to the fused-ring compounds **8** are quite synchronous ($0.17 < \Delta d_{TS/P} < 0.21$, **8d** and **8a**, respectively), whereas the reactions providing the bridged-ring products **9** are decidedly asynchronous ($0.71 < \Delta d_{TS/P} < 0.77$, **9d** and **9b**,**e**, respectively). Noticeably for Diels–Alder cycloadditions to unsymmetrically substituted dienophiles, it has been reported that the more asynchronous is the TS, the lower is the activation barrier.[19] However, owing to the lack of rigorous theoretical justification, such a statement has become merely a sort of empirical rule that holds for several DA reactions.[18,20] To the best of our knowledge, a correlation between synchronicity and activation barrier in dipolar cycloadditions has never been reported and, seeking an analogy between 1,3-dipolar and DA cycloadditions, the most asynchronous pathways should be the favoured ones. However, neither experimental results nor the energies reported in Table 1 can confirm or exclude any correlation between synchronicity and activation barriers. Indeed, the steric hindrance of the R substituent or its ability to establish attractive dispersive interactions can modulate the stability of the regioisomeric TSs, so raising or lowering the activation barriers of the competing cycloadditions. The steric effect emerges by comparing the methyl-substituted **TS-8**,**9a** with the phenyl-substituted **TS-8**,**9e**. Despite the low encumbrance of the methyl group, Figure 2 shows that an unfavourable steric interaction between the methyl and vinyl groups destabilizes **TS-9a** and causes the slight energetic preference computed for **TS-8a**. Together with the thermodynamic preference for **8a**, only one product is thus expected. On the other hand, the phenyl-substituted **TS-8e** presents a steric clash between the *ortho*-hydrogen and the C8-linked hydrogen and such an eclipsed conformation is due to the attempt by the phenyl ring to maximize the attractive π–π interaction with the nitrone benzyl group. Conversely, no unfavourable interactions are observed within **TS-9e**, thus explaining its greater stability. Therefore, because **8e** is the thermodynamic product and **9e** is slightly kinetically favoured, a mixture of regioisomers can be expected. In conclusion, the experimentally observed outcomes can be rationalized for both nitrones **7a** and **7e**.

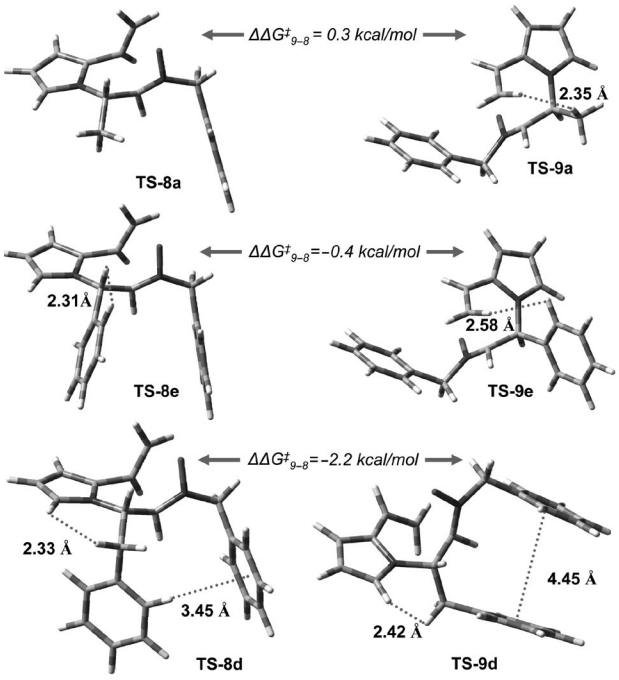


Figure 2. Transition states for the formation of **8a**,**d**,**e** and **9a**,**d**,**e**.

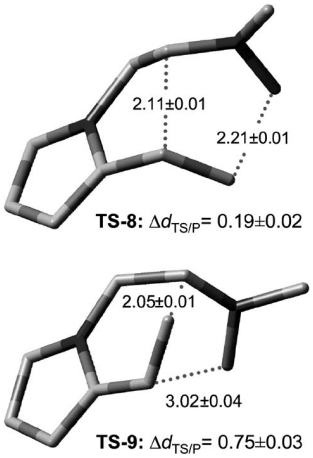
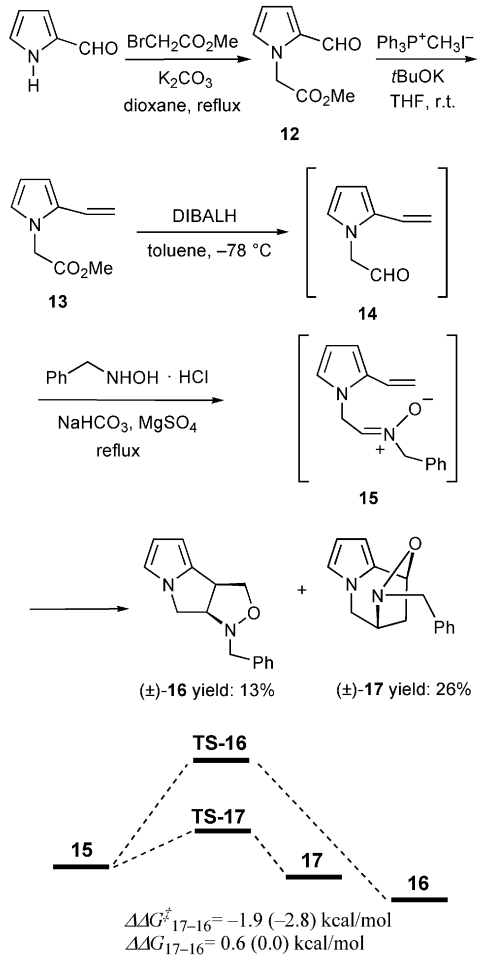


Figure 1. Average TS bond lengths [Å] and degrees of synchronicity $\Delta d_{TS/P}$ for **TS-8** and **TS-9**.

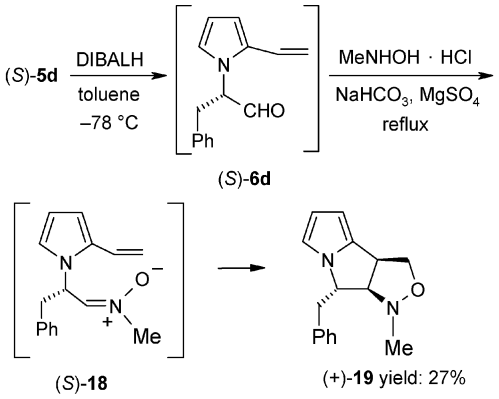
Additional Probing Work

In order to determine the intrinsic stability difference between fused- and bridged-ring TSs, we should eliminate the steric effect of the R substituent. For this reason, we also modelled the two possible cycloaddition paths of the unsubstituted nitrone **15**. The predicted energy difference between the corresponding cycloadducts **16** and **17** was 0.6 kcal/mol in favour of the fused-ring compound **16**, whereas **TS-17** was favoured over **TS-16** with a $\Delta\Delta G^{\ddagger}_{17–16}$ of –1.9 kcal/mol. On the basis of these theoretical calculations, a regioisomeric mixture with the kinetically favoured product **17** predominating can be expected. Moreover, by eliminating the effect of the R substituent, a marked preference for the most asynchronous **TS-17** emerges, which suggests that the relationship between synchronicity and activation barriers observed for DA reactions also holds in principle for 1,3-dipolar cycloadditions. This prediction was confirmed experimentally by the synthetic sequence illustrated in Scheme 2.



Scheme 2. The cycloaddition process and computed energies for the formation of regioisomeric compounds **16** and **17** (solution energies are reported in parentheses).

Turning to the behaviour of the benzyl-substituted nitrone **7d**, steric hindrance by itself is not able to explain the experimental evidence because the fused-ring product **8d** is expected owing to the bulkiness of the benzyl group. However, as shown in Figure 2, **TS-8d** exhibits a T-shaped CH–π interaction between the two aromatic rings that forces the benzylic methylene to clash sterically with the pyrrole 5-H.[21] On the other hand, the PD-shaped π–π interaction between the two aromatic rings observed in **TS-9d** locks the C-5-linked benzyl group into a sterically allowed position, thus justifying the strong preference for the bridged **TS-9d**. Seeking further proof of the role of weak hydrogen or CH–π interactions in determining the regiochemistry of cycloaddition, we hypothesized that the absence of the *N*-benzyl group should unlock the C-5 benzyl and enhance its steric hindrance, thus raising the amount of the fused-ring product. In support of this view, we treated the intermediate **6d** with *N*-methylhydroxylamine and obtained the fused-ring compound **19** as the only product (Scheme 3).



Scheme 3. Cycloaddition reaction of the *N*-methyl-substituted nitrone.

Conclusions

In conclusion, we have described a systematic investigation, both experimental and theoretical, of the intramolecular cycloaddition of a series of variously substituted, pyrrole-based nitrones. Depending on the regiochemistry of the cycloaddition, the final products of the synthetic sequence were 2-benzylamino-2,3-dihydro-1*H*-pyrrolizine-1-methanols or 6-benzylamino-5,6,7,8-tetrahydroindolizin-8-ols. As the regiochemistry of the cycloaddition determines the synthetic targets, its origin was investigated theoretically at different levels of sophistication. Our calculations indicate that the competition between the regioisomeric paths is essentially governed by spatial interactions between the substituents: steric repulsions in the case of alkyl groups and dispersive attractions in the case of aryl groups. Probing experiments were carried out to gain evidence for this rationalization. Furthermore, by constructing the pyrrole nucleus from commercially available L-α-amino acids, we acquired the final products in enantiopure form.

Experimental Section

Melting points were determined by the capillary method with a Büchi B-540 apparatus and are uncorrected. Optical rotations were measured with a Jasco P-1010 polarimeter. NMR spectra were recorded with an AVANCE 400 Bruker spectrometer at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR spectroscopy. Chemical shifts are given as δ values in ppm relative to residual solvent peaks ($CHCl_3$ or C_6H_6) as the internal reference. ^{13}C NMR spectra are ^{1}H-decoupled and the multiplicities were determined by the APT pulse sequence. IR spectra were measured with a Jasco FT/IR 5300 spectrometer. Mass spectra were recorded with a VG-7070 EQ-HF instrument. Elemental analyses were executed using a Perkin-Elmer CHN Analyzer Series II 2400 instrument. Thin-layer chromatographic separations were performed on Merck silica-gel 60-F_{254} precoated plates. Preparative separations were performed by flash chromatography using Merck silica gel (0.035–0.070 mm).

Theoretical Calculations: Reactants **7a**,**e** and **15**, products **8a**,**e**, **9a**,**e**, **16** and **17** and all the corresponding TSs were fully optimized in the gas phase at the HCTH/6-31+G(d) level of theory. As the conformations of the R substituents and the nitrone benzyl group were found to be critical, a rigid conformational search was performed

on TSs and products at the same level of theory. Vibrational frequencies were computed at the same level of theory in order to define optimized geometries as minima (no imaginary frequencies) or transition states (a unique imaginary frequency corresponding to the vibrational stretching of the forming/breaking bonds) and to calculate the ZPVEs and thermochemical corrections to electronic energies (1 atm, 298.15 K). Single-point energies were computed at the HCTH/6-311+G(d,p) level of theory in the gas phase or in toluene with the CPCM solvent model.[22] All calculations were performed with the Gaussian 03 package.[23]

General Procedure for the Preparation of 2-Vinylpyrroles 5a–e: CH_2I_2 (1.0 mL, 12.4 mmol) and $TiCl_4$ (8.0 mL of 1 M solution in CH_2Cl_2) were added to a suspension of zinc (activated in 1 N HCl) (2.4 g, 37.3 mmol) and $PbCl_2$ (104.0 mg, 0.37 mmol) in dry THF (25 mL) under N_2. After stirring for 30 min, a solution of **4a–e** (8.2 mmol) in dry THF (7 mL) was added dropwise and the resultant suspension was stirred overnight at room temperature. The mixture was diluted with AcOEt (25 mL) and washed with a saturated aqueous solution of NH_4Cl (55 mL). The layers were separated and the aqueous phase was extracted with AcOEt (3 × 20 mL). The organic phases were collected, washed with a 1 M solution of $Na_2S_2O_3$ and dried with Na_2SO_4. The solvent was evaporated and the crude mixture was purified by chromatography on a silica gel column with light petroleum/AcOEt (4:1) as eluent to give **5a–e**.

Methyl (*S*)-2-(2-Vinylpyrrol-1-yl)propanoate (5a): Yield 778 mg (53%); colourless oil. IR (Nujol): $\tilde{\nu}$ = 1749 cm^{-1}. $[\alpha]_D^{23}$ = –52.2 (*c* = 0.46, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.75 (d, *J* = 7.2 Hz, 3 H), 3.75 (s, 3 H), 4.97 (q, *J* = 7.2 Hz, 1 H), 5.12 (dd, *J* = 1.0, 11.1 Hz, 1 H), 5.54 (dd, *J* = 1.0, 17.2 Hz, 1 H), 6.22 (t, *J* = 3.2 Hz, 1 H), 6.56 (dd, *J* = 11.1, 17.2 Hz, 1 H), 6.82 (dd, *J* = 1.6, 3.2 Hz, 1 H), 7.02 (dd, *J* = 1.6, 3.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.5 (q), 30.7 (q), 54.1 (d), 107.3 (d), 109.2 (d), 113.0 (t), 119.8 (d), 125.9 (d), 132.5 (s), 172.0 (s) ppm. MS: *m*/*z* = 179 $[M]^+$. $C_{10}H_{13}NO_2$ (179.22): calcd. C 67.02, H 7.31, N 7.82; found C 66.95, H 7.55, N 7.99.

Methyl (*S*)-2-(2-Vinylpyrrol-1-yl)-3-methylbutanoate (5b): Yield 509 mg (30%); colourless oil. IR (Nujol): $\tilde{\nu}$ = 1743 cm^{-1}. $[\alpha]_D^{23}$ = –127.4 (*c* = 0.75, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.73 (d, *J* = 6.6 Hz, 3 H), 1.03 (d, *J* = 6.6 Hz, 3 H), 2.44 (dqq, *J* = 10.5, 6.6, 6.6 Hz, 1 H), 3.74 (s, 3 H), 4.35 (d, *J* = 10.5 Hz, 1 H), 5.11 (dd, *J* = 1.5, 11.2 Hz, 1 H), 5.53 (dd, *J* = 1.5, 17.2 Hz, 1 H), 6.19 (dd, *J* = 3.2, 3.5 Hz, 1 H), 6.36 (dd, *J* = 1.4, 3.2 Hz, 1 H), 6.62 (dd, *J* = 11.2, 17.2 Hz, 1 H), 6.91 (dd, *J* = 1.4, 3.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1 (q), 19.9 (q), 30.7 (q), 52.6 (d), 65.0 (d), 106.7 (d), 109.5 (d), 113.1 (t), 120.3 (d), 125.9 (d), 133.1 (s), 171.2 (s) ppm. MS: *m*/*z* = 207 $[M]^+$. $C_{12}H_{17}NO_2$ (207.27): calcd. C 69.54, H 8.27, N 6.76; found C 69.35, H 8.41, N 6.97.

Methyl (*S*)-2-(2-Vinylpyrrol-1-yl)-4-methylpentanoate (5c): Yield 744 mg (41%); pale-yellow oil. IR (Nujol): $\tilde{\nu}$ = 1748 cm^{-1}. $[\alpha]_D^{23}$ = –65.3 (*c* = 0.29, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.8 Hz, 6 H), 1.29–1.51 (m, 1 H), 1.79–2.10 (m, 2 H), 3.75 (s, 3 H), 4.90 (dd, *J* = 6.1, 9.6 Hz, 1 H), 5.14 (dd, *J* = 1.4, 11.1 Hz, 1 H), 5.56 (dd, *J* = 1.4, 17.2 Hz, 1 H), 6.23 (t, *J* = 3.3 Hz, 1 H), 6.42 (d, *J* = 3.3 Hz, 1 H), 6.63 (dd, *J* = 11.1, 17.2 Hz, 1 H), 6.85 (d, *J* = 3.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1 (q), 23.2 (q), 25.0 (d), 41.7 (t), 52.9 (q), 56.8 (d), 107.1 (d), 109.4 (d), 113.1 (t), 120.3 (d), 125.5 (d), 132.8 (s), 171.9 (s) ppm. MS: *m*/*z* = 221 $[M]^+$. $C_{13}H_{19}NO_2$ (221.30): calcd. C 70.56, H 8.65, N 6.33; found C 70.37, H 8.54, N 6.51.

Methyl (*S*)-2-(2-Vinylpyrrol-1-yl)-3-phenylpropanoate (5d): Yield 565 mg (27%); yellow oil. IR (Nujol): $\tilde{\nu}$ = 1752 cm^{-1}. $[\alpha]_D^{23}$ = –28.8 (*c* = 0.91, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.33 (dd, *J* = 8.7, 13.8 Hz, 1 H), 3.57 (dd, *J* = 6.5, 13.8 Hz, 1 H), 3.76 (s, 3 H), 5.05 (dd, *J* = 6.5, 8.7 Hz, 1 H), 5.09 (dd, *J* = 1.3, 11.1 Hz, 1 H), 5.52 (dd, *J* = 1.3, 17.2 Hz, 1 H), 6.27 (d, *J* = 3.5 Hz, 1 H), 6.42 (d, *J* = 3.5 Hz, 1 H), 6.48 (dd, *J* = 11.1, 17.2 Hz, 1 H), 6.93–6.95 (m, 1 H), 7.08–7.14 (m, 2 H), 7.25–7.35 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.6 (t), 53.0 (q), 60.4 (d), 107.1 (d), 109.5 (d), 113.3 (t), 120.5 (d), 125.3 (d), 127.5 (d), 129.0 (d), 129.3 (d), 132.8 (s), 136.7 (s), 171.0 (s) ppm. MS: *m*/*z* = 255 $[M]^+$. $C_{16}H_{17}NO_2$ (255.32): calcd. C 75.27, H 6.71, N 5.49; found C 75.03, H 6.98, N 5.29.

Methyl (*S*)-2-(2-Vinylpyrrol-1-yl)-2-phenylacetate (5e): Yield 1.25 g (63%); pale-yellow oil. IR (Nujol): $\tilde{\nu}$ = 1745 cm^{-1}. $[\alpha]_D^{23}$ = –4.9 (*c* = 0.67, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.84 (s, 3 H), 5.12 (d, *J* = 11.2 Hz, 1 H), 5.55 (d, *J* = 17.2 Hz, 1 H), 6.08 (s, 1 H), 6.17 (t, *J* = 3.3 Hz, 1 H), 6.42 (d, *J* = 3.3 Hz, 1 H), 6.48 (dd, *J* = 11.2, 17.2 Hz, 1 H), 6.65 (d, *J* = 3.2 Hz, 1 H), 7.28–7.30 (m, 2 H), 7.40–7.44 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.2 (q), 62.7 (d), 107.7 (d), 109.1 (d), 113.2 (t), 122.0 (d), 125.3 (d), 128.4 (d), 129.3 (d), 129.4 (d), 132.8 (s), 135.3 (s), 170.4 (s) ppm. MS: *m*/*z* = 241 $[M]^+$. $C_{15}H_{15}NO_2$ (241.29): calcd. C 74.67, H 6.27, N 5.80; found C 74.75, H 6.36, N 5.89.

General Procedure for the One-Pot Reduction of 5a–e and 13 and Cycloaddition of the Nitrones Arising from the Aldehyde Intermediates: Preparation of mixture A: a solution of **5a–e** (or **13**) (4 mmol) in dry toluene (75 mL) was cooled to –78 °C under nitrogen and a 1.5 M DIBAL-H solution (3.5 mL, 5.2 mmol) was added dropwise. The mixture was stirred at –78 °C for 1 h. Preparation of mixture B: a suspension of *N*-benzylhydroxylamine hydrochloride (0.64 g, 4 mmol), $NaHCO_3$ (0.68 g, 8 mmol) and $MgSO_4$ (4.44 g, 37 mmol) in toluene (60 mL) was stirred for 15 min at room temperature. Mixture B was slowly added to mixture A and the resultant suspension was heated at reflux for 24 h. After cooling, the mixture was washed with 1 M HCl (150 mL) and the aqueous layer was extracted with AcOEt (3 × 150 mL). The collected organic phases were washed with H_2O, 5% aqueous solution of $NaHCO_3$ and dried with Na_2SO_4. The solvent was evaporated and the crude mixture was purified by chromatography on a silica gel column with light petroleum/AcOEt (4:1) as eluent to give **8a–e** and **9d,e** [or **16** and **17**, or **19** (in the case of **19**, *N*-methylhydroxylamine hydrochloride was used in the preparation of mixture B)].

(3a*S*,8*S*,8a*R*)-1-Benzyl-8-methyl-3,3a,8,8a-tetrahydro-1*H*-isoxazolo[4,3-*a*]pyrrolizine (8a): Yield 244 mg (24%); colourless oil. $[\alpha]_D^{23}$ = +78.1 (*c* = 0.46, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 6.6 Hz, 3 H), 3.85, 4.17 (AB system, *J* = 12.8 Hz, 2 H), 3.89 (dd, *J* = 4.5, 7.7 Hz, 1 H), 3.91 (dd, *J* = 3.7, 8.0 Hz, 1 H), 4.15 (dq, *J* = 3.7, 6.6 Hz, 1 H), 4.17 (dt, *J* = 4.5, 7.7 Hz, 1 H), 4.33 (t, *J* = 7.7 Hz, 1 H), 5.84 (d, *J* = 3.3 Hz, 1 H), 6.25 (dd, *J* = 2.9, 3.3 Hz, 1 H), 6.50 (d, *J* = 2.9 Hz, 1 H), 7.30–7.45 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6 (q), 46.0 (d), 60.7 (t), 62.8 (d), 72.4 (t), 81.6 (d), 99.9 (d), 112.8 (d), 113.3 (d), 127.5 (d), 128.3 (d), 129.5 (d), 136.8 (s), 137.0 (s) ppm. MS: *m*/*z* = 254 $[M]^+$. $C_{16}H_{18}N_2O$ (254.33): calcd. C 75.56, H 7.13, N 11.01; found C 75.39, H 6.97, N 10.79.

(3a*S*,8*S*,8a*R*)-1-Benzyl-8-isopropyl-3,3a,8,8a-tetrahydro-1*H*-isoxazolo[4,3-*a*]pyrrolizine (8b): Yield 192 mg (17%); colourless oil. $[\alpha]_D^{23}$ = +59.6 (*c* = 0.13, $CHCl_3$). ^1H NMR (400 MHz, C_6D_6): δ = 0.55 (d, *J* = 6.8 Hz, 3 H), 0.61 (d, *J* = 6.8 Hz, 3 H), 1.78 (dqq, *J* = 3.0, 6.8, 6.8 Hz, 1 H), 3.66 (dd, *J* = 2.6, 8.2 Hz, 1 H), 3.69, 3.96 (AB system, *J* = 12.5 Hz, 2 H), 3.74 (ddd, *J* = 3.7, 7.5, 8.2 Hz, 1 H), 3.85 (dd, *J* = 3.7, 7.8 Hz, 1 H), 3.96 (dd, *J* = 7.5, 7.8 Hz, 1 H), 4.02 (dd, *J* = 2.6, 3.0 Hz, 1 H), 6.02 (dd, *J* = 2.9, 3.2 Hz, 1 H), 6.49

(dd, J = 1.2, 2.9 Hz, 1 H), 6.58 (dd, J = 1.2, 3.2 Hz, 1 H), 7.23–7.45 (m, 5 H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 17.2 (q), 18.2 (q), 32.3 (d), 46.7 (d), 60.9 (t), 68.6 (d), 72.6 (t), 75.8 (d), 98.9 (d), 113.1 (d), 113.4 (d), 128.0 (d), 128.8 (d), 129.7 (d), 137.0 (s), 137.9 (s) ppm. MS: m/z = 282 $[M]^+$. $C_{18}H_{22}N_2O$ (282.39): calcd. C 76.56, H 7.85, N 9.92; found C 76.55, H 8.07, N 9.79.

(3a*S*,8*S*,8a*R*)-1-Benzyl-8-isobutyl-3,3a,8,8a-tetrahydro-1*H*-isoxazolo[4,3-*a*]pyrrolizine (8c): Yield 308 mg (26%); white crystals; m.p. 82–84 °C (diisopropyl ether). $[\alpha]_D^{23}$ = +119.8 (c = 0.49, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (d, J = 6.3 Hz, 3 H), 0.91 (d, J = 6.2 Hz, 3 H), 1.26–1.45 (m, 2 H), 1.58–1.71 (m, 1 H), 3.84, 4.13 (AB system, J = 12.3 Hz, 2 H), 3.92 (dd, J = 3.0, 8.3 Hz, 1 H), 3.94 (d, J = 7.8 Hz, 1 H), 4.11–4.15 (m, 1 H), 4.18 (dd, J = 3.0, 7.6, 7.8 Hz, 1 H), 4.32 (d, J = 7.6 Hz, 1 H), 5.83 (d, J = 3.1 Hz, 1 H), 6.24 (d, J = 3.1 Hz, 1 H), 6.50 (br. s, 1 H), 7.28–7.43 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.7 (q), 23.3 (q), 24.9 (d), 45.2 (t), 46.0 (d), 60.8 (t), 62.1 (d), 72.5 (t), 80.0 (d), 99.4 (d), 113.0 (d), 113.2 (d), 128.1 (d), 128.9 (d), 129.8 (d), 136.9 (s), 137.1 (s) ppm. MS: m/z = 296 $[M]^+$. $C_{19}H_{24}N_2O$ (296.42): calcd. C 76.99, H 8.16, N 9.45; found C 77.11, H 8.33, N 9.27.

(3a*S*,8*S*,8a*R*)-1,8-Dibenzyl-3,3a,8,8a-tetrahydro-1*H*-isoxazolo[4,3-*a*]pyrrolizine (8d): Yield 343 mg (26%); white crystals; m.p. 84–86 °C (diisopropyl ether). $[\alpha]_D^{23}$ = +108.9 (c = 0.47, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.88 (dd, J = 6.6, 14.0 Hz, 1 H), 3.01 (dd, J = 5.8, 14.0 Hz, 1 H), 3.67 (d, J = 12.8 Hz, 1 H), 3.86 (dd, J = 2.6, 8.2 Hz, 1 H), 3.96–3.97 (m, 2 H), 4.03 (d, J = 12.8 Hz, 1 H), 4.28 (dd, J = 3.6, 8.2 Hz, 1 H), 4.43 (dd, J = 5.8, 6.6 Hz, 1 H), 5.82 (d, J = 3.3 Hz, 1 H), 6.24 (d, J = 3.3 Hz, 1 H), 6.34 (dd, J = 2.6, 3.3 Hz, 1 H), 6.93–6.95 (m, 2 H), 7.25–7.29 (m, 3 H), 7.35–7.41 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.1 (t), 46.4 (d), 60.7 (t), 64.3 (d), 72.6 (t), 78.8 (d), 99.7 (d), 113.6 (d), 115.4 (d), 127.4 (d), 128.2 (d), 129.1 (d), 129.8 (d), 130.0 (d), 130.5 (d), 137.1 (s), 137.2 (s), 137.7 (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 80.08, H 6.69, N 8.59.

(3a*S*,8*S*,8a*R*)-1-Benzyl-8-phenyl-3,3a,8,8a-tetrahydro-1*H*-isoxazolo-[4,3-*a*]pyrrolizine (8e): Yield 202 mg (16%); white crystals; m.p. 93–95 °C (diisopropyl ether). $[\alpha]_D^{23}$ = +39.4 (c = 0.08, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (d, J = 12.9 Hz, 1 H), 3.99 (dd, J = 3.1, 7.9 Hz, 1 H), 4.07 (dd, J = 3.3, 7.5 Hz, 1 H), 4.15 (d, J = 12.9 Hz, 1 H), 4.27 (ddd, J = 3.1, 7.4, 7.5 Hz, 1 H), 4.34 (dd, J = 7.4, 7.9 Hz, 1 H), 5.19 (d, J = 3.3 Hz, 1 H), 5.93 (d, J = 3.3 Hz, 1 H), 6.30 (dd, J = 2.4, 3.3 Hz, 1 H), 6.39 (d, J = 2.4 Hz, 1 H), 6.87–6.90 (m, 2 H), 7.26–7.38 (m, 5 H), 7.38–7.40 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.5 (d), 60.8 (t), 68.0 (d), 72.4 (t), 83.6 (d), 99.6 (d), 113.9 (d), 114.3 (d), 126.3 (d), 128.0 (d), 128.3 (d), 128.9 (d), 129.2 (d), 129.5 (d), 136.8 (s), 138.1 (s), 144.3 (s) ppm. MS: m/z = 316 $[M]^+$. $C_{21}H_{20}N_2O$ (316.41): calcd. C 79.72, H 6.37, N 8.85; found C 79.90, H 6.16, N 8.99.

(1*S*,4*R*,5*S*)-3,5-Dibenzyl-4,5-dihydro-1*H*,3*H*-1,4-methanopyrrolo-[1,2-*e*][1,2,5]oxadiazepine (9d): Yield 224 mg (17%); colourless oil. $[\alpha]_D^{23}$ = +61.7 (c = 0.68, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.28 (m, 2 H), 2.85 (dd, J = 9.8, 14.3 Hz, 1 H), 3.23 (dd, J = 5.3, 14.3 Hz, 1 H), 3.60 (br. s, 1 H), 3.75, 4.18 (AB system, J = 12.6 Hz, 2 H), 4.48 (dd, J = 5.3, 9.8 Hz, 1 H), 5.20 (t, J = 2.6 Hz, 1 H), 6.00 (dd, J = 1.5, 3.5 Hz, 1 H), 6.12 (d, J = 3.5 Hz, 1 H), 6.59 (d, J = 1.5 Hz, 1 H), 6.98–7.01 (m, 2 H), 7.19–7.28 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.1 (t), 40.8 (t), 61.2 (d), 63.0 (d), 63.3 (t), 71.4 (d), 104.7 (d), 108.9 (d), 119.4 (d), 127.1 (d), 127.9 (d),128.8 (d), 129.0 (d), 129.2 (d), 129.5 (d), 131.8 (s), 135.6 (s), 137.0 (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 79.98, H 6.56, N 8.24.

(1*S*,4*R*,5*S*)-3-Benzyl-5-phenyl-4,5-dihydro-1*H*,3*H*-1,4-methanopyrrolo[1,2-*e*][1,2,5]oxadiazepine (9e): Yield 126 mg (10%); white crystals; m.p. 118–120 °C (diisopropyl ether). $[\alpha]_D^{23}$ = +7.5 (c = 0.33, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.19–2.23 (m, 1 H), 2.34 (d, J = 11.4 Hz, 1 H), 3.66 (d, J = 4.7 Hz, 1 H), 3.87, 4.33 (AB system, J = 12.6 Hz, 2 H), 5.29 (d, J = 4.7 Hz, 1 H), 5.34 (s, 1 H), 6.11 (dd, J = 1.1, 3.4 Hz, 1 H), 6.16 (dd, J = 3.0, 3.4 Hz, 1 H), 6.44 (dd, J = 1.1, 3.0 Hz, 1 H), 6.73–6.75 (m, 3 H), 7.25–7.44 (m, 5 H), 7.47–7.49 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.3 (t), 63.5 (t), 66.3 (d), 66.7 (d), 71.3 (d), 104.7 (d), 109.1 (d), 120.8 (d), 126.8 (d), 128.1 (d), 128.2 (d), 129.0 (d), 129.1 (d), 129.6 (d), 132.7 (s), 137.6 (s), 140.5 (s) ppm. MS: m/z = 330 $[M]^+$. $C_{21}H_{20}N_2O$ (316.41): calcd. C 79.72, H 6.37, N 8.85; found C 79.61, H 6.61, N 9.02.

(3a*R,8a*S**)-1-Benzyl-3,3a,8,8a-tetrahydro-1*H*-isoxazolo[4,3-*a*]-pyrrolizine (16):** Yield 125 mg (13%); colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.87–3.94 (m, 3 H), 4.10 (dd, J = 7.6, 11.1 Hz, 1 H), 4.14 (dd, J = 4.0, 12.9 Hz, 1 H), 4.19 (dd, J = 3.8, 7.8 Hz, 1 H), 4.30–4.38 (m, 2 H), 5.86 (d, J = 3.3 Hz, 1 H), 6.25 (dd, J = 2.9, 3.3 Hz, 1 H), 6.52 (d, J = 2.9 Hz, 1 H), 7.29–7.45 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.9 (d), 51.7 (t), 60.7 (t), 72.3 (t), 73.9 (d), 99.8 (d), 113.4 (d), 114.2 (d), 128.1 (d), 129 (d), 129.5 (d), 136.9 (s), 137.7 (s) ppm. MS: m/z = 240 $[M]^+$. $C_{15}H_{16}N_2O$ (240.31): calcd. C 74.97, H 6.71, N 11.66; found C 75.11, H 6.54, N 11.52.

(1*R,4*S**)-3-Benzyl-4,5-dihydro-1*H*,3*H*-1,4-methanopyrrolo[1,2-*e*]-[1,2,5]oxadiazepine (17):** Yield 250 mg (26%); white crystals; m.p. 116–118 °C (diisopropyl ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.18 (d, J = 11.2 Hz, 1 H), 2.48 (ddd, J = 5.3, 5.6, 11.2 Hz, 1 H), 3.70–3.77 (ddd, J = 2.2, 2.8, 5.3 Hz, 1 H), 3.81 (d, J = 12.7 Hz, 1 H), 3.97 (dd, J = 2.8, 11.8 Hz, 1 H), 4.05 (dd, J = 2.2, 11.8 Hz, 1 H), 4.23 (d, J = 12.7 Hz, 1 H), 5.22 (d, J = 5.3 Hz, 1 H), 5.97 (dd, J = 1.5, 3.5 Hz, 1 H), 6.08 (dd, J = 3.2, 3.5 Hz, 1 H), 6.52 (dd, J = 1.8, 3.2 Hz, 1 H), 7.23–7.45 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.2 (t), 52.8 (t), 58.4 (d), 63.5 (t), 71.3 (d), 104.6 (d), 108.8 (d), 120.2 (d), 128.0 (d), 128.9 (d), 129.6 (d), 132.3 (s), 137.6 (s) ppm. MS: m/z = 240 $[M]^+$. $C_{15}H_{16}N_2O$ (240.31): calcd. C 74.97, H 6.71, N 11.66; found C 74.79, H 6.93, N 11.61.

(3a*S*,8*S*,8a*R*)-8-Benzyl-1-methyl-3,3a,8,8a-tetrahydro-1*H*-isoxazolo-[4,3-*a*]pyrrolizine (19): Yield 274 mg (27%); colourless oil. $[\alpha]_D^{23}$ = +96.7 (c = 0.40, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.52 (s, 3 H), 3.04 (dd, J = 7.1, 13.9 Hz, 1 H), 3.16 (dd, J = 6.4, 13.9 Hz, 1 H), 3.71–3.86 (m, 2 H), 3.93–3.99 (m, 1 H), 4.24 (t, J = 7.9 Hz, 1 H), 4.51 (br. s, 1 H), 5.79 (d, J = 3.3 Hz, 1 H), 6.22 (dd, J = 2.6, 3.3 Hz, 1 H), 6.37 (d, J = 2.6 Hz, 1 H), 7.12–7.18 (m, 2 H), 7.23–7.37 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.8 (t), 43.7 (q), 46.4 (d), 64.4 (d), 72.0 (t), 81.4 (d), 99.5 (d), 113.4 (d), 124.4 (d), 127.5 (d), 129.1 (d), 129.8 (d), 137.2 (s), 137.7 (s) ppm. MS: m/z = 254 $[M]^+$. $C_{16}H_{18}N_2O$ (254.33): calcd. C 75.56, H 7.13, N 11.01; found C 75.26, H 7.31, N 10.75.

General Procedure for the Isoxazolidine Ring-Opening with $LiAlH_4$: A 1 M solution of $LiAlH_4$ (0.90 mL) in THF was added to a solution of **8a**–**e** or **9d**,**e** (0.14 mmol) in dry THF (2 mL) under nitrogen. The resultant solution was heated at reflux for 24 h and then, after cooling, MeOH (18 mL) was added dropwise. After concentration, a solution of AcONa (690 mg, 8.37 mmol) in H_2O (3.5 mL) was added and the mixture was extracted with $CHCl_3$ (4 × 4 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by chromatography on a silica gel column with light petroleum/AcOEt (2:1) as eluent to give **10a**–**e** or **11d**,**e**, respectively.

(1*S*,2*R*,3*S*)-(2-Benzylamino-3-methyl-2,3-dihydro-1*H*-pyrrolizin-1-yl)methanol (10a): Yield 15 mg (42%); colourless oil. IR (Nujol): $\tilde{\nu}$ = 3320, 2910 cm^{-1}. $[\alpha]_D^{23}$ = –5.3 (*c* = 0.33, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.50 (d, *J* = 6.3 Hz, 3 H), 2.12 (br. s, 2 H, missing after deuteriation), 3.44 (dt, *J* = 7.2, 5.8 Hz, 1 H), 3.58 (dd, *J* = 6.8, 7.2 Hz, 1 H), 3.87 (d, *J* = 5.8 Hz, 2 H), 3.92, 4.01 (AB system, *J* = 13.0 Hz, 2 H), 4.05 (qd, *J* = 6.3, 6.8 Hz, 1 H), 5.88 (d, *J* = 3.4 Hz, 1 H), 6.23 (dd, *J* = 2.5, 3.4 Hz, 1 H), 6.60 (d, *J* = 2.5 Hz, 1 H), 7.30–7.39 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.7 (q), 43.5 (d), 53.4 (t), 59.0 (d), 63.4 (t), 70.9 (d), 100.6 (d), 111.9 (d), 113.0 (d), 127.9 (d), 128.6 (d), 129.0 (d), 135.2 (s), 139.9 (s) ppm. MS: *m*/*z* = 256 $[M]^+$. $C_{16}H_{20}N_2O$ (256.35): calcd. C 74.97, H 7.86, N 10.93; found C 75.22, H 7.61, N 11.10.

(1*S*,2*R*,3*S*)-(2-Benzylamino-3-isopropyl-2,3-dihydro-1*H*-pyrrolizin-1-yl)methanol (10b): Yield 25 mg (63%); colourless oil. IR (Nujol): $\tilde{\nu}$ = 3310, 2902 cm^{-1}. $[\alpha]_D^{23}$ = +21.6 (*c* = 0.10, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.9 Hz, 3 H), 0.98 (d, *J* = 6.9 Hz, 3 H), 2.08 (dt, *J* = 4.8, 6.9 Hz, 1 H), 2.30 (br. s, 2 H, missing after deuteriation), 3.51 (d, *J* = 5.1 Hz, 1 H), 3.79 (d, *J* = 8.4 Hz, 1 H), 3.83, 3.95 (AB system, *J* = 12.9 Hz, 2 H), 3.88 (d, *J* = 8.4 Hz, 1 H), 3.97 (d, *J* = 5.1 Hz, 1 H), 4.01 (d, *J* = 4.8 Hz, 1 H), 5.80 (d, *J* = 3.4 Hz, 1 H), 6.23 (dd, *J* = 2.7, 3.4 Hz, 1 H), 6.61 (d, *J* = 2.7 Hz, 1 H), 7.28–7.40 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4 (q), 19.5 (q), 32.2 (d), 42.3 (d), 51.8 (t), 61.9 (t), 65.5 (d), 68.8 (d), 98.6 (d), 112.4 (s), 112.5 (d), 115.0 (d), 125.4 (d), 128.7 (d), 129.4 (d), 135.3 (s) 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 75.97, H 8.80, N 9.68.

(1*S*,2*R*,3*S*)-(2-Benzylamino-3-isobutyl-2,3-dihydro-1*H*-pyrrolizin-1-yl)methanol (10c): Yield 24 mg (59%); pale-yellow oil. IR (Nujol): $\tilde{\nu}$ = 3328, 2915 cm^{-1}. $[\alpha]_D^{23}$ = +20.1 (*c* = 0.14, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 6.6 Hz, 3 H), 1.03 (d, *J* = 6.6 Hz, 3 H), 1.53 (ddd, *J* = 6.5, 7.2, 13.8 Hz, 1 H), 1.68 (ddd, *J* = 5.9, 7.5, 13.8 Hz, 1 H), 1.92 (ddt, *J* = 6.5, 7.5, 6.6 Hz, 1 H), 2.16 (br. s, 2 H, missing after deuteriation), 3.50 (d, *J* = 7.1 Hz, 1 H), 3.65 (dd, *J* = 5.5, 7.1 Hz, 1 H), 3.86–3.96 (m, 4 H), 4.11 (ddd, *J* = 5.5, 5.9, 7.2 Hz, 1 H), 5.85 (d, *J* = 3.2 Hz, 1 H), 6.22 (dd, *J* = 2.5, 3.2 Hz, 1 H), 6.63 (d, *J* = 2.5 Hz, 1 H), 7.29–7.37 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.8 (q), 23.6 (q), 30.1 (t), 30.7 (d), 41.7 (d), 53.1 (t), 61.7 (d), 62.8 (t), 69.7 (d), 100.2 (d), 112.1 (d), 114.1 (d), 127.9 (d), 128.6 (d), 129.1 (d), 135.4 (s), 139.8 (s) ppm. MS: *m*/*z* = 298 $[M]^+$. $C_{19}H_{26}N_2O$ (298.43): calcd. C 76.47, H 8.78, N 9.39; found C 76.23, H 8.89, N 9.51.

(1*S*,2*R*,3*S*)-(3-Benzyl-2-benzylamino-2,3-dihydro-1*H*-pyrrolizin-1-yl)methanol (10d): Yield 24 mg (52%); colourless oil. IR (Nujol): $\tilde{\nu}$ = 3305, 2912 cm^{-1}. $[\alpha]_D^{23}$ = +20.2 (*c* = 0.30, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.21 (br. s, 2 H, missing after deuteriation), 3.02 (dd, *J* = 7.2, 13.8 Hz, 1 H), 3.17 (dd, *J* = 6.4, 13.8 Hz, 1 H), 3.40 (dd, *J* = 7.0, 4.9 Hz, 1 H), 3.67–3.75 (m, 3 H), 3.84 (dd, *J* = 7.0, 12.2 Hz, 1 H), 3.89 (dd, *J* = 4.9, 12.2 Hz, 1 H), 4.33 (dd, *J* = 6.4, 7.2 Hz, 1 H), 5.85 (d, *J* = 3.3 Hz, 1 H), 6.20 (dd, *J* = 2.6, 3.3 Hz, 1 H), 6.46 (d, *J* = 2.6 Hz, 1 H), 7.11–7.13 (m, 2 H), 7.19–7.21 (m, 2 H), 7.26–7.39 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.1 (t), 41.6 (d), 53.0 (t), 63.3 (t), 64.3 (d), 68.7 (d), 100.3 (d), 112.2 (d), 113.8 (d), 127.4 (d), 127.8 (d), 128.7 (d), 128.9 (d), 129.3 (d), 129.6 (d), 135.6 (s), 137.5 (s), 139.5 (s) ppm. MS: *m*/*z* = 332 $[M]^+$. $C_{22}H_{24}N_2O$ (332.44): calcd. C 79.48, H 7.28, N 8.43; found C 79.22, H 7.41, N 8.55.

(1*S*,2*R*,3*S*)-(2-Benzylamino-3-phenyl-2,3-dihydro-1*H*-pyrrolizin-1-yl)methanol (10e): Yield 16 mg (35%); colourless oil. IR (Nujol): $\tilde{\nu}$ = 3308, 2900 cm^{-1}. $[\alpha]_D^{23}$ = –5.9 (*c* = 0.14, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.44 (br. s, 2 H, missing after deuteriation), 3.53 (dt, *J* = 6.0, 5.8 Hz, 1 H), 3.85–3.89 (m, 3 H), 3.96 (d, *J* = 6.5 Hz, 2 H), 5.06 (d, *J* = 6.5 Hz, 1 H), 5.97 (d, *J* = 2.6 Hz, 1 H), 6.27 (d, *J* = 2.6 Hz, 1 H), 6.61 (s, 1 H), 7.16 (dd, *J* = 5.6, 7.1 Hz, 4 H), 7.26 (d, *J* = 7.1 Hz, 2 H), 7.38 (d, *J* = 5.6 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.1 (d), 53.1 (t), 63.3 (t), 67.8 (d), 72.7 (d), 100.7 (d), 112.5 (d), 114.5 (d), 127.4 (d), 127.7 (d), 128.4 (d), 128.7 (d), 128.9 (d), 129.3 (d), 135.9 (s), 139.5 (s), 139.9 (s) ppm. MS: *m*/*z* = 318 $[M]^+$. $C_{21}H_{22}N_2O$ (318.42): calcd. C 79.21, H 6.96, N 8.80; found C 79.33, H 6.74, N 8.59.

(5*S*,6*R*,8*S*)-5-Benzyl-6-benzylamino-5,6,7,8-tetrahydroindolizin-8-ol (11d): Yield 15 mg (33%); colourless oil. IR (Nujol): $\tilde{\nu}$ = 3324, 2906 cm^{-1}. $[\alpha]_D^{23}$ = +5.1 (*c* = 0.36, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.12 (ddd, *J* = 2.9, 6.8, 14.9 Hz, 1 H), 2.30 (ddd, *J* = 3.2, 6.4, 14.9 Hz, 1 H), 2.34 (br. s, 2 H, missing after deuteriation), 2.86 (dd, *J* = 8.5, 13.9 Hz, 1 H), 3.03 (dd, *J* = 5.6, 13.9 Hz, 1 H), 3.67–3.72 (m, 1 H), 3.70, 3.88 (AB system, *J* = 13.0 Hz, 2 H), 4.31 (dd, *J* = 5.6, 8.5 Hz, 1 H), 4.86 (dd, *J* = 2.9, 3.2 Hz, 1 H), 6.20 (dd, *J* = 2.9, 3.5 Hz, 1 H), 6.23 (d, *J* = 3.5 Hz, 1 H), 6.48 (d, *J* = 2.9 Hz, 1 H), 7.03–7.06 (m, 2 H), 7.13–7.15 (m, 2 H), 7.23–7.38 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.4 (t), 51.9 (t), 53.9 (d), 61.8 (d), 62.7 (d), 63.1 (t), 107.2 (d), 109.1 (d), 119.9 (d), 127.3 (d), 127.7 (d), 128.5 (d), 129.0 (d), 129.2 (d), 129.5 (d), 131.2 (s), 137.7 (s), 139.4 (s) ppm. MS: *m*/*z* = 332 $[M]^+$. $C_{22}H_{24}N_2O$ (332.45): calcd. C 79.48, H 7.28, N 8.43; found C 79.67, H 7.09, N 8.19.

(5*S*,6*R*,8*S*)-6-Benzylamino-5-phenyl-5,6,7,8-tetrahydroindolizin-8-ol (11e): Yield 13 mg (30%); colourless oil. IR (Nujol): $\tilde{\nu}$ = 3304, 2915 cm^{-1}. $[\alpha]_D^{23}$ = –4.8 (*c* = 0.05, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.01–2.07 (m, 2 H), 2.25 (br. s, 2 H, missing after deuteriation), 3.34 (dd, *J* = 2.9, 6.8 Hz, 1 H), 3.90, 4.07 (AB system, *J* = 13.1 Hz, 2 H), 4.97 (t, *J* = 4.0 Hz, 1 H), 5.27 (d, *J* = 2.9 Hz, 1 H), 6.26 (dd, *J* = 3.2, 3.5 Hz, 1 H), 6.33 (dd, *J* = 1.9, 3.5 Hz, 1 H), 6.65 (dd, *J* = 1.9, 3.2 Hz, 1 H), 6.64–6.66 (m, 2 H), 7.25–7.40 (m, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.1 (t), 58.9 (d), 63.1 (d), 64.3 (d), 68.5 (t), 107.1 (d), 109.7 (d), 121.0 (d), 126.5 (d), 127.8 (d), 128.1 (d), 128.6 (d), 129.1 (d), 129.2 (d), 135.6 (s), 139.4 (s), 142.1 (s) ppm. MS: *m*/*z* = 318 $[M]^+$. $C_{21}H_{22}N_2O$ (318.42): calcd. C 79.21, H 6.96, N 8.80; found C 79.02, H 7.24, N 8.97.

Supporting Information (see also the footnote on the first page of this article): Cartesian coordinates and energies of the stationary points.

Acknowledgments

The authors thank the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR) (First and PRIN) for financial support and the Centro Interuniversitario Lombardo per l'Elaborazione Automatica (CILEA) for computational facilities.

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Received: December 21, 2007
Published Online: April 9, 2008

