

From Amino Acids to Enantiopure Bicyclic Isoxazolidinylpyridin-4(1*H*)-ones through Intramolecular Nitrone Cycloadditions

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Homochiral bicyclic isoxazolidinylpyridin-4(1*H*)-ones have been synthesised by an intramolecular nitrone cycloaddition process, starting from homochiral β -amino acids. Stereoselection at C² or C³ of the acyclic substrate appears to give the best results in the control of the stereochemistry of the new

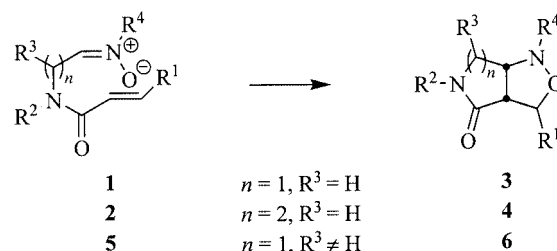
formed chiral centres. The synthetic approach has been further directed towards functionalised piperidones.

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Introduction

Intramolecular nitrone–alkene cycloadditions have received a great deal of attention as a useful methodology for the formation of the intriguing frameworks occurring in natural products and biologically interesting compounds.^[1–8] The key feature of the approach is that suitable elaboration of the primary cycloadducts has proved to be a practical strategy for different heterocyclic ring systems:^[9,10] in particular, the nitrogen–oxygen bond can readily be cleaved to yield variously functionalised amino alcohols. In this context, the insertion of an amido group in the tether connecting the nitrone moiety to the dipolarophilic double bond has allowed a valuable route to functionalised medium-sized lactams, and in this way functionalised γ - and δ -lactams have been synthesised by starting from 5-hexenyl-**(1)**^[11] and 6-heptenyl nitrones **(2)**,^[12] respectively (Scheme 1). The reaction showed complete diastereoselectivity, with fused hexahydro-4*H*-pyrrolo[3,4-*c*]isoxazol-4-ones **(3)** and hexahydroisoxazolo[4,3-*c*]pyridin-4(1*H*)-ones **(4)** being formed, each possessing a *cis* junction between the isoxazolidine and the lactam rings.

The insertion of a chiral centre into the starting substrate could cause asymmetric induction, giving rise to the formation of new chiral centres with definite configurations in the cycloadducts.^[13,14] In fact, a stereocentre located in the position α to the nitrone functionality completely controls the stereochemical outcome of the pericyclic process start-



Scheme 1.

ing from **5**, which exclusively affords compound **6** with simultaneous introduction of three stereocentres (Scheme 1).

In this paper we have extended the intramolecular nitrone cycloaddition process to a series of intermediate *N*-oxides **12** generated from compounds **11**, each containing a stereocenter outside the tether, on the amide nitrogen atom or in the chain connecting the alkene and the dipole moieties, in the α or β position with respect to the nitrone functionality. Stereoselection at C² or C³ of the acyclic substrate appears to give the best results in the control of the stereochemistry of the newly formed chiral centres.

Our interest in this reaction is further stimulated by the potential for useful functionalisation of the fused system by cleavage of the isoxazolidine ring and formation of substituted piperidones. As reported, δ -lactams have been evaluated as good substrates for the development of new classes of anti-infectives and other inhibitors of serine protease such as elastases.^[15] Elastases are current targets for medicinal chemistry; δ -lactams act by acylating a serine hydroxy group in the catalytic centre of a bacterial protease, with the same reactivity as β -lactam antibiotics.^[16]

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Results and Discussion

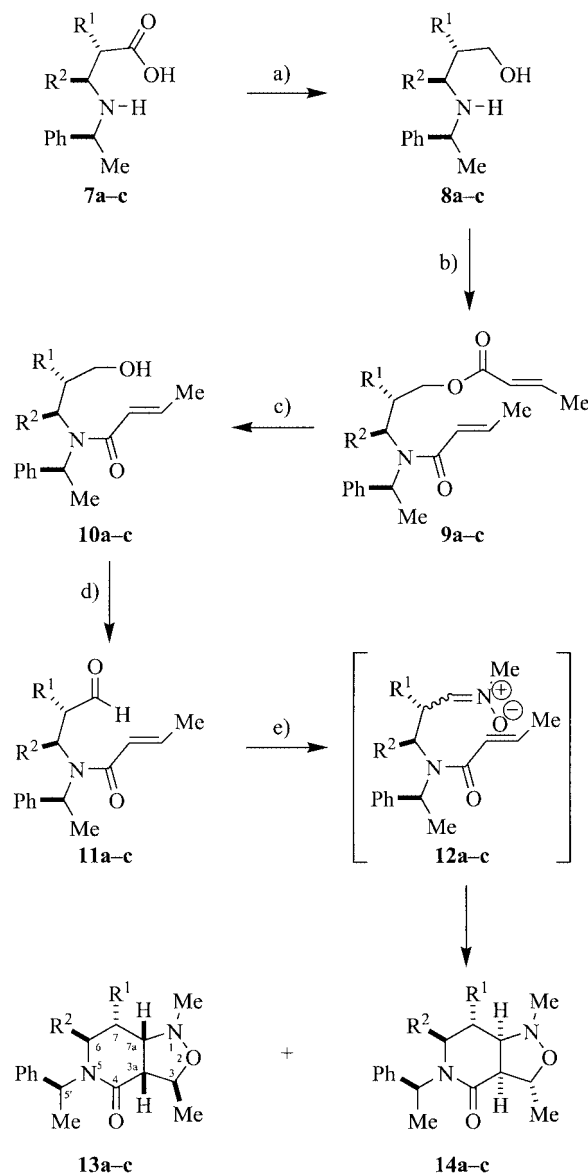
The β -amino acid **7a**, containing a chiral centre attached to the nitrogen atom, was synthesised by standard procedures.^[17] Compound **7a** was then reduced to 3-[(1*S*)-1-phenylethyl]amino]propan-1-ol (**8a**), and further treatment with (*E*)-but-2-enoyl chloride gave (after selective hydrolysis of the intermediate ester **9a** with K_2CO_3 in aqueous methanol) the corresponding amido alcohol **10a**. Attempts to introduce the but-2-enoyl group selectively at the nitrogen atom resulted in lower yields. Swern-like oxidation of **10a** afforded the aldehyde **11a**, which was transformed by treatment with *N*-methylhydroxylamine into the corresponding hexahydroisoxazolo[4,3-*c*]pyridin-4(1*H*)-ones **13a** and **14a**, in a 1:1 relative ratio, via the not isolated nitron **12a** (Scheme 2).

The obtained compounds were characterised by analytical and spectroscopic data. High-resolution mass spectra showed the correct molecular ions, and the IR absorptions of the carbonyl groups are at 1680–1670 cm^{-1} , consistently with δ -lactams. The 1H NMR spectrum of compound **13a** shows the H^3 proton at $\delta = 4.01$ as a doublet of quartets, the H^{3a} proton resonates as a doublet of doublets at $\delta = 2.86$, while H^{7a} gives rise to a doublet of doublets at $\delta = 3.40$. The methylene protons at C^7 appear as an indistinct multiplet centred at $\delta = 1.60$, while the H^6 protons resonate as multiplets at $\delta = 3.01$ and 2.80. Furthermore, the 1H NMR spectrum shows the methyl group at C^3 as a doublet at $\delta = 1.53$.

Diagnostic resonances for the diastereoisomer **14a** are only slightly different from the above values, except for H^3 , which resonates as a multiplet at $\delta = 4.30$, and for H^{3a} , which resonates as a doublet of doublets at $\delta = 2.72$.

The investigated 1,3-dipolar cycloaddition showed complete regioselectivity: no bridged products were detected in the crude reaction mixture. Moreover, the process was found to be stereospecific, but lacking in any diastereofacial selectivity. The stereochemical information present in the dipolarophile moiety is completely retained in the obtained cycloadducts and the relative stereochemistry at C^3 and C^{3a} in the formed isoxazolidine ring is *trans*, as predetermined by the alkene geometry. Furthermore, the ring junction between the isoxazolidine ring and the lactam five-membered ring is always *cis*, as evidenced by NOE experiments. Irradiation of the H^{3a} resonance in compounds **13** and **14** thus gives rise to strong positive NOE effects on H^{7a} and the methyl substituent at C^3 , indicating a *cis* topological relationship. Straightforwardly, the configurations of compounds **13** and **14** are interchangeable.

The effects of the introduction of a stereocentre into the β position with respect to the nitron functionality were investigated, starting from (3*S*)-3-methyl-3-[(1*S*)-1-phenylethyl]amino]propan-1-ol (**8b**), prepared from amino acid **7b**.^[18] Treatment of the β -amido aldehyde **11b**, prepared by the above procedure, with methylhydroxylamine gave rise to nitron intermediate **12b**, which spontaneously cyclised to the bicyclic compound **13b** as the only obtained cycloadduct (Scheme 2). The stereochemistry of **13b** was assigned



Amino acid	R ¹	R ²	Yield %	13/14 Ratio
7a	H	H	82	1:1
7b	H	Me	82	1:0
7c	Me	H	78	0:1

Scheme 2. a) $LiAlH_4$, THF, 0 °C to reflux, 12 h; b) (*E*)-but-2-enoyl chloride, Et_3N , DCM, 0 °C, 1 h and then room temp., 6 h; c) 6% aqueous K_2CO_3 , MeOH, room temp., 3 h; d) bis(trichloromethyl) carbonate, DCM, DMSO, Et_3N , –78 °C to room temp. 1 h; e) $MeNH_2 \cdot HCl$, Et_3N , EtOH, reflux, 24 h.

by NOE measurements: the positive NOE effects observed for H^{7a} and methyl groups at C^3 and C^6 when H^{3a} was irradiated are clearly indicative of their *cis* relationship.

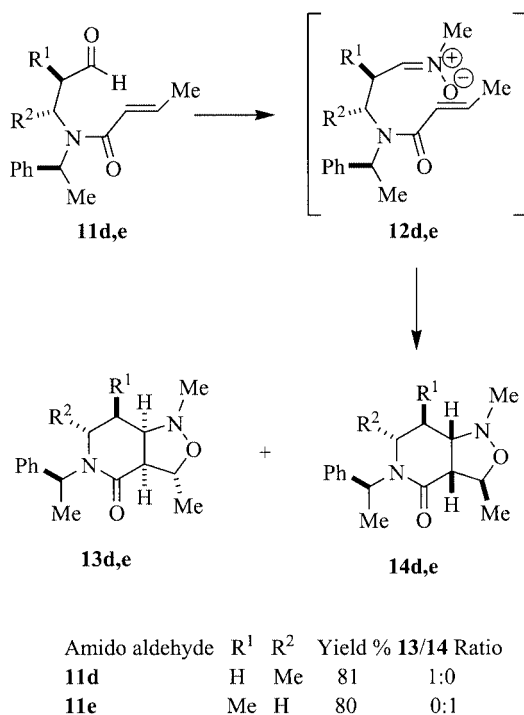
The cycloaddition process was found to proceed with complete stereochemical control, furnishing homochiral compound **13b** from homochiral starting material. Thus, in this reaction, the stereocentre at the α position with respect to the amido group can effectively control the formation of the new contiguous stereocentres and one of the eight pos-

sible stereoisomers is produced in a highly selective fashion.

Analogous results were obtained when the chiral centre was located in the α position with respect to the nitron group. The intramolecular cycloaddition process starting from (2*S*)-2-methyl-3-[(1*S*)-1-phenylethyl]amino]propan-1-ol (**8c**)^[19] exclusively afforded the cycloadduct **14c** (Scheme 2).

The stereochemical outcomes of the investigated intramolecular cycloaddition processes clearly indicate that the presence of the chiral centre in the α or β position promotes a total diastereofacial selectivity: the obtained enantiomerically pure cycloadducts **13b** and **14c** each show a *cis* relationship for H^{3a}, H^{7a} and methyl groups at C³ and C⁶.

As a further confirmation, changes of the configurations at C² and C³, as in compounds **11d** and **11e**, respectively [derived from the (2*R*)- and (3*R*)-propan-1-ols **8d** and **8e**], resulted exclusively in the compounds **13d** and **14e** (Scheme 3).



Scheme 3.

The observed results were also confirmed by semiempirical calculations. From inspection of Dreiding models, two different transition state conformers—in the *E* or in the *Z* configurations—are possible. These should produce compounds **13** if the alkene moiety attacks the *Re* face of the nitron or compounds **14** if the attack takes place from the *Si* face (Figure 1).

In order to achieve quantitative information, three-dimensional models of all the possible TSs were full geometrically optimised by use of the PM3 semiempirical Hamiltonian as implemented in the Chem3D graphic interface to MOPAC. In all cases the (*E*)-TSs proved to be more stable (3–6 kcal mol⁻¹) than the corresponding (*Z*)-ones,^[20] due to the steric hindrance of the two methyl groups at C¹ and C³.

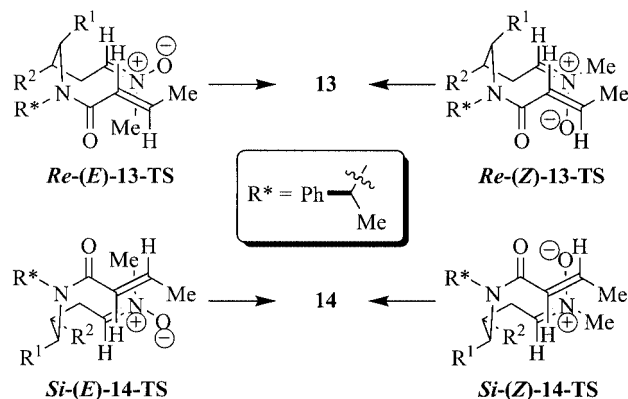


Figure 1. Transition state structures for compounds **13** and **14**; in the case of compounds **d** and **e** all stereocentres, except for the *N*-auxiliary, must be inverted.

Thus, only the values for the (*E*)-TSs are reported (Table 1) together with the calculated **13:14** ratio, obtained in accord with the Boltzmann equation.

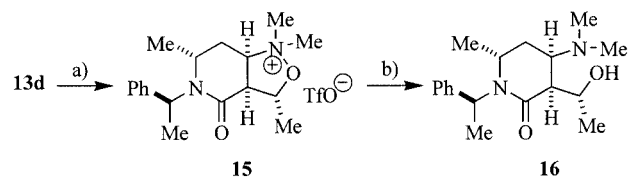
Table 1. PM3 formation enthalpies for transition states (*E*)-**13** and (*E*)-**14**.

	ΔH_f (<i>E</i>)- 13 -TS	ΔH_f (<i>E</i>)- 14 -TS	Calculated 13:14 ratio
a	30.79 ^[a]	30.67	45:55
b	26.32	30.61	99.93:0.07
c	30.47	25.17	0.01:99.99
d	27.05	29.09	96.84:3.16
e	30.06	25.18	0.03:99.97

[a] All values are in kcal mol⁻¹.

The data reported in Table 1 are fully in agreement with the experimental results.

The selective ring cleavage of the isoxazolidine nucleus allows an easy synthetic route to homochiral functionalised piperidones. Thus, compound **16** was obtained by treatment of **13d** with methyl trifluoromethanesulfonate, in dry CCl₄ at 0 °C, followed by hydrogenolysis with 5% palladium on CaCO₃ in dry MeOH at 60 °C for 12 h (yields 90%) (Scheme 4).



Scheme 4. (a) Methyl triflate, CCl₄, 0 °C, 2 h; (b) 5% Pd/CaCO₃, gaseous H₂, MeOH, 60 °C, 12 h.

Conclusions

In conclusion, the reported intramolecular nitron cycloaddition process, starting from β -amino acids, affords homochiral bicyclic isoxazolidinylpyridin-4(1*H*)-ones, which could be usefully manipulated towards functionalised piperidones.

It has been reported that medium-sized lactams are the least susceptible lactams to hydrolysis,^[21] so the synthesised compounds could be valuable candidates as potential elastase inhibitors through the formation of stable acyl–enzyme complexes.

Experimental Section

General Remarks: All melting points are uncorrected. Elemental analyses were carried out on a C. Erba 1106 elemental analyzer. IR spectra were recorded on a Perkin–Elmer Paragon 500 FT-IR Spectrometer in potassium bromide discs. ¹H and ¹³C NMR spectra were recorded on a Varian Unity Inova 300 instrument in deuterated DMSO. Chemical shifts are expressed in ppm from CDCl₃ (δ = 7.26 ppm for ¹H and 77.0 ppm for ¹³C). Thin-layer chromatographic separations were performed on Merck silica gel 60-F₂₅₄ precoated aluminium plates. Preparative separations were carried out by flash column chromatography with Merck silica gel (0.035–0.070 mm, eluent CHCl₃/MeOH, 95:5).

General Procedure for the Preparation of Compounds 10a–e: A solution of (*E*)-but-2-enoyl chloride (3.93 mL, 41 mmol) in dry CH₂Cl₂ (20 mL) was added dropwise at 0 °C to a stirred solution containing compounds **8a–e** (20.0 mmol) and triethylamine (5.71 mL, 41 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 6 h. At the end of this time, the mixture was extracted with dichloromethane, washed with 10% aqueous NaHCO₃, dried (Na₂CO₃) and evaporated under reduced pressure. Aqueous K₂CO₃ (6%, 25 mL) was added to a solution of the crude amido ester **9a–e** in MeOH (50 mL). The mixture was left stirring until TLC showed the disappearance of the starting material. After removal of the solvent under reduced pressure, the residue was subjected to silica gel flash chromatography (eluent MeOH/CHCl₃, 5:95).

(2*E*)-*N*-((3-Hydroxypropyl)-*N*-((1*S*)-1-phenylethyl)but-2-enamide (10a): 4.20 g, 85% yield; white oil. ¹H NMR (CHCl₃, 300 MHz): δ = 1.60 (d, *J* = 6.9 Hz, 3 H), 1.80 (d, *J* = 6.6 Hz, 3 H), 1.85 (m, 2 H), 3.32 (m, 2 H), 4.87 (m, 3 H), 6.09 (d, *J* = 15.0 Hz, 1 H), 6.40 (dq, *J* = 6.6, 15.0 Hz, 1 H), 7.17–7.30 (m, 5 H) ppm. ¹³C NMR (CDCl₃, 75 MHz): δ = 19.0, 20.0, 30.5, 47.2, 60.1, 73.5, 127.4, 128.2, 129.5, 129.8, 130.0, 132.0, 140.3, 140.6, 171.8 ppm. IR (KBr): $\tilde{\nu}$ = 3600, 3200, 1675, 1560, 1420, 1370, 1060, 980, 700 cm⁻¹. C₁₅H₂₁NO₂: C 72.84, H 8.56, N 5.66%; found C 72.61, H 5.34, N 5.35%. Exact mass calculated for C₁₅H₂₁NO₂: 247.3308; found 247.3302.

(2*E*)-*N*-((1*S*)-3-Hydroxy-1-methylpropyl)-*N*-((1*S*)-1-phenylethyl)-but-2-enamide (10b): 4.60 g, 88% yield; white oil. ¹H NMR (CDCl₃, 300 MHz): δ = 1.15 (d, *J* = 6.4 Hz, 3 H), 1.65 (d, *J* = 6.5 Hz, 3 H), 1.70 (d, *J* = 6.4 Hz, 3 H), 1.95 (m, 2 H), 3.02 (br. s, 1 H), 3.55 (m, 2 H), 4.95 (q, *J* = 6.5 Hz, 1 H), 5.05 (d, *J* = 14.7 Hz, 1 H), 6.95 (m, 1 H), 6.85 (dq, *J* = 6.4, 14.7 Hz, 1 H), 7.35 (m, 5 H) ppm. ¹³C NMR (CDCl₃, 75 MHz): δ = 18.3, 19.2, 19.5, 42.0, 61.2, 74.3, 78.4, 127.4, 128.9, 130.6, 130.8, 132.9, 133.0, 141.0, 141.6, 170.9. IR (KBr): $\tilde{\nu}$ = 3600, 3200, 1680, 1565, 1420, 1425, 1370, 1060, 980, 700 cm⁻¹. Anal. Calcd. for C₁₆H₂₃NO₂: C 73.52, H 8.87, N 5.35; found C 73.60, H 8.90, N 5.30. Exact mass calculated for C₁₆H₂₃NO₂: 261.3594; found 261.3589.

(2*E*)-*N*-((2*S*)-3-Hydroxy-2-methylpropyl)-*N*-((1*S*)-1-phenylethyl)-but-2-enamide (10c): 4.44 g, 85% yield; white oil. ¹H NMR (CDCl₃, 300 MHz): mixture of rotamers, δ = 0.95 (d, *J* = 6.3 Hz, 3 H), 1.60 (d, *J* = 6.5 Hz, 3 H), 1.90 (d, *J* = 6.2 Hz, 3 H), 2.01 (br. s, 1 H), 2.17 (m, 1 H), 2.92 (m, 1 H), 3.10 (m, 1 H), 3.49–3.56 (m, 2 H),

5.05 (q, *J* = 6.5 Hz, 1 H), 6.40 (d, *J* = 14.7 Hz, 1 H), 6.85 (dq, *J* = 6.2, 14.7 Hz, 1 H), 7.35 (m, 5 H) ppm. ¹³C NMR (CDCl₃, 75 MHz): δ = 13.7, 16.9, 21.2, 35.0, 47.9, 50.7, 67.4, 128.4, 128.9, 129.6, 130.8, 132.9, 133.0, 141.0, 141.5, 170.2 ppm. IR (KBr): $\tilde{\nu}$ = 3600, 3200, 1680, 1565, 1420, 1425, 1370, 1060, 980, 700 cm⁻¹. Anal. Calcd. for C₁₆H₂₃NO₂: C 73.52, H 8.87, N 5.35; found C 73.60, H 8.90, N 5.30. Exact mass calculated for C₁₆H₂₃NO₂: 261.3594; found 261.3589.

(2*E*)-*N*-((1*R*)-3-Hydroxy-1-methylpropyl)-*N*-((1*S*)-1-phenylethyl)-but-2-enamide (10d): 4.44 g, 85% yield; white oil. ¹H NMR (CDCl₃, 300 MHz): δ = 1.34 (d, *J* = 6.8 Hz, 3 H), 1.62 (d, *J* = 6.9 Hz, 3 H), 1.81 (d, *J* = 6.5 Hz, 3 H), 1.88 (m, 2 H), 3.25 (m, 2 H), 5.05 (q, *J* = 6.9 Hz, 1 H), 5.25 (m, 1 H), 5.98 (d, *J* = 14.3 Hz, 1 H), 6.83 (dq, *J* = 6.5, 14.3 Hz, 1 H) ppm. ¹³C NMR (CDCl₃, 75 MHz): δ = 18.2, 19.0, 19.9, 41.5, 60.0, 76.5, 78.1, 127.4, 128.1, 129.4, 129.8, 129.9, 132.1, 140.1, 140.6, 170.7 ppm. IR (KBr): $\tilde{\nu}$ = 3600, 3200, 1680, 1565, 1420, 1370, 1060, 980, 700 cm⁻¹. C₁₆H₂₃NO₂: C 73.52, H 8.87, N 5.35; found C 73.46, H 8.85, N 5.31. Exact mass calculated for C₁₆H₂₃NO₂: 261.3594; found 261.3589.

(2*E*)-*N*-((2*R*)-3-Hydroxy-2-methylpropyl)-*N*-((1*S*)-1-phenylethyl)-but-2-enamide (10e): 4.55 g, 87% yield; white oil. ¹H NMR (CDCl₃, 300 MHz): mixture of rotamers, δ = 0.95 (d, *J* = 6.9 Hz, 3 H), 1.55 (d, *J* = 5.8 Hz, 3 H), 1.90 (d, *J* = 6.9 Hz, 3 H), 2.58 (m, 1 H), 3.17 (m, 1 H), 3.43 (m, 1 H), 3.63 (m, 1 H), 5.10 (q, *J* = 5.8 Hz, 1 H), 6.35 (d, *J* = 14.7 Hz, 1 H), 6.95 (dq, *J* = 6.9, 14.7 Hz, 1 H), 7.35 (m, 5 H) ppm. ¹³C NMR (CDCl₃, 75 MHz): δ = 15.6, 19.3, 19.5, 36.7, 45.6, 56.0, 63.2, 122.0, 126.0, 126.2, 127.6, 128.8, 131.4, 141.3, 142.6, 169.2 ppm. IR (KBr): $\tilde{\nu}$ = 3600, 3200, 1685, 1570, 1420, 1370, 1060, 980, 700 cm⁻¹. Anal. Calcd. for C₁₆H₂₃NO₂: C 73.52, H 8.87, N 5.35; found C 73.50, H 8.84, N 5.31. Exact mass calculated for C₁₆H₂₃NO₂: 261.3594; found 261.3590.

General Procedure for the Preparation of Aldehydes 11a–e: Anhydrous DMSO (1.7 mL, 24 mmol) was added at –78 °C to a stirred solution of bis(trichloromethyl) carbonate (1.19 g, 4 mmol) in dry dichloromethane (12 mL). The reaction mixture was stirred for 15 min and then a solution of **10a–e** (4 mmol) in dichloromethane (8 mL) was slowly added at the same temperature. After the mixture had been stirred for 15 min, triethylamine (3.90 mL, 28 mmol) in dichloromethane (16 mL) was added dropwise, the temperature being maintained below –70 °C. After the addition, the resulting suspension was stirred at –78 °C for 5 min and then the acetone/dry ice bath was removed. The reaction mixture was stirred at room temp. for 1 h and the solvent was removed under reduced pressure. The obtained residue was extracted with dichloromethane, washed with water, dried with sodium sulfate and flash chromatographed on silica gel (eluent CHCl₃/MeOH, 97:3).

(2*E*)-*N*-((3-Oxopropyl)-*N*-((1*S*)-1-phenylethyl)but-2-enamide (11a): 755 mg, 77% yield; yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ = 1.64 (d, *J* = 6.4 Hz, 3 H), 1.93 (d, *J* = 6.6 Hz, 3 H), 2.98 (m, 2 H), 3.98 (m, 2 H), 5.35 (q, *J* = 6.4 Hz, 1 H), 6.40 (d, *J* = 14.5 Hz, 1 H), 6.45 (dq, *J* = 6.6, 14.5 Hz, 1 H), 7.35 (m, 5 H), 9.63 (s, 1 H) ppm. ¹³C NMR (CDCl₃, 75 MHz): δ = 17.3, 18.3, 36.6, 51.5, 55.8, 121.8, 126.9, 127.3, 128.0, 128.7, 139.5, 142.3, 168.0, 195.1 ppm. IR (KBr): $\tilde{\nu}$ = 3060, 2980, 2960, 1735, 1665, 1600, 1400, 1200, 970, 760, 700, 680 cm⁻¹. C₁₅H₁₉NO₂: C 73.44, H 7.81, N 5.70; found C 73.35, H 7.76, N 5.74. Exact mass calculated for C₁₅H₁₉NO₂: 245.3214; found 245.3250.

(2*E*)-*N*-((1*S*)-1-Methyl-3-oxopropyl)-*N*-((1*S*)-1-phenylethyl)but-2-enamide (11b): 716 mg, 69% yield; yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ = 1.24 (d, *J* = 6.5 Hz, 3 H), 1.69 (d, *J* = 6.4 Hz, 3 H), 1.95 (d, *J* = 6.4 Hz, 3 H), 2.85 (ddd, *J* = 1.4, 7.5, 9.2 Hz, 1 H), 3.33 (ddd, *J* = 1.4, 7.5, 9.1 Hz, 1 H), 5.07 (q, *J* = 6.4 Hz, 1 H), 5.10

(ddq, $J = 6.5, 9.1, 9.2$ Hz, 1 H), 6.40 (d, $J = 15.1$ Hz, 1 H), 6.95 (dq, $J = 6.4, 15.1$ Hz, 1 H), 7.40 (m, 5 H), 9.77 (t, $J = 1.4$ Hz, 1 H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 17.5, 17.7, 18.1, 40.5, 45.8, 62.1, 123.8, 127.8, 127.8, 128.0, 129.5, 132.4, 139.6, 142.0, 172.3, 200.0$ ppm. IR (KBr): $\tilde{\nu} = 3060, 2980, 2960, 1735, 1645, 1600, 1400, 1200, 970, 760, 700, 680$ cm^{-1} . $\text{C}_{16}\text{H}_{21}\text{NO}_2$: C 74.09, H 8.16, N 5.40; found C 74.13, H 8.13, N 5.35. Exact mass calculated for $\text{C}_{16}\text{H}_{21}\text{NO}_2$: 259.3435; found 259.3433.

(2E)-N-((2S)-2-Methyl-3-oxopropyl)-N-((1S)-1-phenylethyl)but-2-enamide (11c): 695 mg, 67% yield; yellow oil. ^1H NMR (CDCl_3 , 300 MHz): $\delta = 0.95$ (d, $J = 6.2$ Hz, 3 H), 1.40 (d, $J = 6.1$ Hz, 3 H), 1.90 (d, $J = 6.5$ Hz, 3 H), 3.40 (m, 1 H), 3.97 (m, 2 H), 5.35 (q, $J = 10.0$ Hz, 1 H), 6.40 (d, $J = 13.5$ Hz, 1 H), 6.95 (dq, $J = 6.5, 13.5$ Hz, 1 H), 7.40 (m, 5 H), 9.45 (d, $J = 0.9$ Hz, 1 H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 19.4, 19.8, 211, 40.0, 56.2, 57.1, 121.5, 123.9, 127.7, 127.9, 128.0, 129.5, 132.3, 139.5, 141.9, 167.5, 200.0$ ppm. IR (KBr): $\tilde{\nu} = 3060, 2980, 2960, 1735, 1685, 1600, 1400, 1200, 970, 760, 700, 680$ cm^{-1} . $\text{C}_{16}\text{H}_{21}\text{NO}_2$: C 74.09, H 8.16, N 5.40; found C 74.10, H 8.09, N 5.35. Exact mass calculated for $\text{C}_{16}\text{H}_{21}\text{NO}_2$: 259.3435; found 259.3432.

(2E)-N-((1R)-1-Methyl-3-oxopropyl)-N-((1S)-1-phenylethyl)but-2-enamide (11d): 674 mg, 65% yield; yellow oil. ^1H NMR (CDCl_3 , 300 MHz): $\delta = 1.43$ (d, $J = 6.5$ Hz, 3 H), 1.67 (d, $J = 6.7$ Hz, 3 H), 1.93 (d, $J = 6.6$ Hz, 3 H), 3.21 (m, 2 H), 5.02 (m, 1 H), 5.07 (q, $J = 6.7$ Hz, 1 H), 5.10 (m, 1 H), 6.23 (d, $J = 15.1$ Hz, 1 H), 6.95 (dq, $J = 6.6, 15.1$ Hz, 1 H), 7.35 (m, 5 H), 9.25 (dd, $J = 1.3, 1.2$ Hz, 1 H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 17.7, 18.5, 19.9, 40.0, 45.9, 66.0, 123.9, 127.7, 127.9, 128.0, 129.5, 132.3, 139.5, 141.9, 167.5, 200.0$ ppm. IR (KBr): $\tilde{\nu} = 3060, 2980, 2960, 1735, 1645, 1600, 1400, 1200, 970, 760, 700, 680$ cm^{-1} . $\text{C}_{16}\text{H}_{21}\text{NO}_2$: C 74.09, H 8.16, N 5.40; found C 74.10, H 8.14, N 5.33. Exact mass calculated for $\text{C}_{16}\text{H}_{21}\text{NO}_2$: 259.3435; found 259.3437.

(2E)-N-((2S)-2-Methyl-3-oxopropyl)-N-((1S)-1-phenylethyl)but-2-enamide (11e): 622 mg, 60% yield; yellow oil. ^1H NMR (CDCl_3 , 300 MHz): $\delta = 0.97$ (d, $J = 6.8$ Hz, 3 H), 1.62 (d, $J = 6.1$ Hz, 3 H), 1.82 (d, $J = 6.5$ Hz, 3 H), 3.20 (m, 1 H), 4.10 (m, 2 H), 5.15 (q, $J = 6.1$ Hz, 1 H), 6.22 (d, $J = 13.5$ Hz, 1 H), 6.95 (dq, 1 H, $J = 6.5, 13.5$ Hz), 7.20 (m, 5 H), 9.45 (d, $J = 1.0$ Hz, 1 H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 19.3, 19.5, 19.6, 39.5, 55.8, 56.0, 122.0, 126.0, 127.6, 128.8, 131.4, 140.3, 142.6, 169.6, 193.9$ ppm. IR (KBr): $\tilde{\nu} = 3060, 2980, 2965, 1735, 1680, 1600, 1400, 1200, 970, 760, 700, 680$ cm^{-1} . $\text{C}_{16}\text{H}_{21}\text{NO}_2$: C 74.09, H 8.16, N 5.40; found C 74.14, H 8.13, N 5.43. Exact mass calculated for $\text{C}_{16}\text{H}_{21}\text{NO}_2$: 259.3435; found 259.3428.

General Procedure for the Preparation of 13a, 13b, 13d, 14a and 14c:

A mixture containing the aldehyde **11a–e** (1.0 mmol), triethylamine (1.5 mL, 1.1 mmol) and methylhydroxylamine hydrochloride (92 mg, 1.1 mmol) in absolute ethanol (20 mL), was heated at reflux for 24 h. At the end of this time the solvent was evaporated under reduced pressure and the residue was subjected to silica flash chromatography (eluent MeOH/ CHCl_3 , 2:8).

(3S,3aR,7aS)-1,3-Dimethyl-5-((1S)-1-phenylethyl)hexahydroisoxazolo[4,3-c]pyridin-4(1H)-one (13a): 112 mg, 41% yield; white oil, $[\alpha]_D^{25} = -30.26$ ($c = 0.53$; CHCl_3). ^1H NMR (CDCl_3 , 500 MHz): $\delta = 1.53$ (d, $J = 5.7$ Hz, 3 H), 1.55 (d, $J = 5.9$ Hz, 3 H), 1.60 (m, 2 H, H^7), 2.68 (s, 3 H, $N\text{-CH}_3$), 2.80 (m, 1 H, H^6), 2.86 (dd, $J = 7.5, 12.6$ Hz, 1 H, H^{3a}), 3.01 (m, 1 H, H^6), 3.40 (dt, $J = 6.1, 12.6$ Hz, 1 H, H^{7a}), 4.01 (dq, $J = 5.7, 7.5$ Hz, 1 H, H^3), 6.06 (q, $J = 5.9$ Hz, 1 H, $\text{H}^{5'}$), 7.35 (m, 5 H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 15.7, 16.6, 20.1, 27.0, 38.7, 44.3, 56.6, 67.1, 79.0, 128.3, 128.7, 129.5, 129.6, 130.8, 142.9, 169.8$ ppm. IR (KBr): $\tilde{\nu} = 1672$ cm^{-1} . $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_2$: C 70.04, H 8.08, N 10.21; found C 70.14, H 8.15,

N 10.10. Exact mass calculated for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_2$: 274.3630; found 274.3624.

(3R,3aS,7aR)-1,3-Dimethyl-5-((1S)-1-phenylethyl)hexahydroisoxazolo[4,3-c]pyridin-4(1H)-one (14a): 112 mg, 41% yield; white oil, $[\alpha]_D^{25} = -20.76$ ($c = 0.62$; CHCl_3). ^1H NMR (CDCl_3 , 500 MHz): $\delta = 1.55$ (d, $J = 5.7$ Hz, 3 H), 1.57 (d, $J = 5.8$ Hz, 3 H), 1.59 (m, 2 H, H^7), 2.71 (s, 3 H, $N\text{-CH}_3$), 2.72 (dd, $J = 7.3, 12.4$ Hz, 1 H, H^{3a}), 2.82 (m, 1 H, H^6), 3.12 (m, 1 H, H^6), 3.41 (dt, $J = 6.2, 12.4$ Hz, 1 H, H^{7a}), 4.30 (dq, $J = 5.7, 7.3$ Hz, 1 H, H^3), 6.04 (q, $J = 5.9$ Hz, 1 H, $\text{H}^{5'}$), 7.35 (m, 5 H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 15.5, 16.4, 26.4, 27.9, 37.7, 44.5, 51.1, 67.0, 78.6, 128.3, 128.4, 129.6, 130.8, 136.8, 141.3, 169.9$ ppm. IR (KBr): $\tilde{\nu} = 1671$ cm^{-1} . $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_2$: C 70.04, H 8.08, N 10.21; found C 70.01, H 8.20, N 10.25. Exact mass calculated for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_2$: 274.3630; found 274.3620. The configurations of compounds **13a** and **14a** are interchangeable.

(3S,3aR,6S,7aS)-1,3,6-Trimethyl-5-((1S)-1-phenylethyl)hexahydroisoxazolo[4,3-c]pyridin-4(1H)-one (13b): 236 mg, 82% yield; white oil, $[\alpha]_D^{25} = -54.96$ ($c = 0.74$; CHCl_3). ^1H NMR (CDCl_3 , 500 MHz): $\delta = 0.53$ (d, $J = 6.9$ Hz, 3 H), 1.43 (d, $J = 7.2$ Hz, 3 H), 1.48 (d, $J = 6.3$ Hz, 3 H), 1.70 (m, 1 H, H^7), 1.75 (ddd, $J = 0.8, 7.2, 12.6$ Hz, 1 H, H^7), 2.59 (s, 3 H, $N\text{-CH}_3$), 2.68 (dd, $J = 7.8, 10.5$ Hz, 1 H, H^{3a}), 2.91 (ddd, $J = 7.2, 7.5, 10.5$ Hz, 1 H, H^{7a}), 3.56 (m, 1 H, H^6), 4.25 (dq, $J = 7.2, 7.8$ Hz, 1 H, H^3), 5.94 (q, $J = 6.3$ Hz, 1 H, $\text{H}^{5'}$), 7.35 (m, 5 H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 15.6, 17.4, 19.6, 29.7, 47.2, 50.6, 53.4, 64.8, 76.2, 127.7, 128.2, 128.3, 128.4, 128.4, 140.1, 169.3$ ppm. IR (KBr): $\tilde{\nu} = 1675$ cm^{-1} . $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2$: C 70.80, H 8.38, N 9.71; found C 80.74, H 8.35, N 9.46. Exact mass calculated for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2$: 288.3847; found 288.3841.

(3S,3aR,7S,7aS)-1,3,7-Trimethyl-5-((1S)-1-phenylethyl)hexahydroisoxazolo[4,3-c]pyridin-4(1H)-one (14c): 225 mg, 78% yield; white oil. $[\alpha]_D^{25} = -65.12$ ($c = 0.43$; CHCl_3). ^1H NMR (CDCl_3 , 500 MHz): $\delta = 0.62$ (d, $J = 7.1$ Hz, 3 H), 1.48 (d, $J = 7.1$ Hz, 3 H), 1.50 (d, $J = 6.0$ Hz, 3 H), 1.71 (dddq, $J = 2.3, 3.3, 7.1, 7.5$ Hz, 1 H, H^7), 2.51 (dd, $J = 2.3, 8.8$ Hz, 1 H, H^{7a}), 2.61 (dd, $J = 3.4, 12.0$ Hz, 1 H, H^6), 2.66 (s, 3 H, $N\text{-CH}_3$), 2.86 (dd, $J = 7.2, 8.8$ Hz, 1 H, H^{3a}), 3.50 (dd, $J = 3.3, 12.0$ Hz, 1 H, H^6), 3.96 (dq, $J = 6.2, 7.2$ Hz, 1 H, H^3), 6.10 (q, $J = 7.0$ Hz, 1 H, $\text{H}^{5'}$), 7.32 (m, 5 H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 15.3, 15.8, 19.3, 29.0, 42.1, 43.6, 49.7, 54.0, 72.2, 77.5, 127.2, 127.6, 127.8, 128.3, 128.5, 139.8, 168.4$ ppm. IR (KBr): $\tilde{\nu} = 1674$ cm^{-1} . $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2$: C 70.80, H 8.38, N 9.71; found C 70.77, H 8.40, N 9.75. Exact mass calculated for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2$: 288.3847; found 288.3845.

(3R,3aS,6R,7aR)-1,3,6-Trimethyl-5-((1S)-1-phenylethyl)hexahydroisoxazolo[4,3-c]pyridin-4(1H)-one (13d): 233 mg, 81% yield; white oil, $[\alpha]_D^{25} = -15.11$ ($c = 1.50$; CHCl_3). ^1H NMR (CDCl_3 , 500 MHz): $\delta = 1.27$ (d, $J = 6.5$ Hz, 3 H), 1.53 (d, $J = 6.3$ Hz, 3 H), 1.58 (d, $J = 6.6$ Hz, 3 H), 2.70 (m, 2 H, H^7), 2.63 (s, 3 H, $N\text{-CH}_3$), 2.83 (dd, $J = 7.5, 9.9$ Hz, 1 H, H^{3a}), 3.02 (ddd, $J = 7.8, 7.5, 9.9$ Hz, 1 H, H^{7a}), 3.40 (ddq, $J = 5.9, 6.5, 6.8$ Hz, 1 H, H^6), 3.98 (dq, $J = 6.3, 7.5$ Hz, 1 H, H^3), 6.06 (q, $J = 6.6$ Hz, 1 H, $\text{H}^{5'}$), 7.32 (m, 5 H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 17.5, 19.8, 19.9, 21.5, 33.0, 47.3, 49.8, 52.9, 64.8, 76.8, 127.3, 127.9, 128.0, 129.4, 140.0, 169.8$ ppm. IR (KBr): $\tilde{\nu} = 1675$ cm^{-1} . $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2$: C 70.80, H 8.38, N 9.71; found C 70.75, H 8.57, N 9.75. Exact mass calculated for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2$: 288.3845; found 288.3860.

(3R,3aS,7R,7aR)-1,3,7-Trimethyl-5-((1S)-1-phenylethyl)hexahydroisoxazolo[4,3-c]pyridin-4(1H)-one (14e): 231 mg, 80% yield; white oil, $[\alpha]_D^{25} = -79.11$ ($c = 3.16$; CHCl_3). ^1H NMR (CDCl_3 , 500 MHz): $\delta = 1.01$ (d, $J = 7.0$ Hz, 3 H), 1.48 (d, $J = 7.0$ Hz, 3 H), 1.51 (d, $J = 5.9$ Hz, 3 H), 1.75 (dddq, $J = 2.9, 3.3, 4.3, 7.0$ Hz, 1 H, H^7), 2.58 (ddd, $J = 1.1, 2.9, 9.3$ Hz, 1 H, H^{7a}), 2.66 (s, 3 H, $N\text{-CH}_3$), 2.70

(ddd, $J = 1.1, 4.3, 12.8$ Hz, 1 H, H^6), 2.89 (dd, $J = 7.9, 9.3$ Hz, 1 H, H^{3a}), 3.12 (dd, $J = 3.3, 12.8$ Hz, 1 H, H^6), 3.98 (dq, $J = 5.9, 7.9$ Hz, 1 H, H^3), 6.05 (q, $J = 7.0$ Hz, 1 H, $H^{5'}$), 7.52 (m, 5 H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 15.0, 16.3, 19.2, 29.7, 43.7, 43.8, 49.6, 54.1, 72.4, 77.6, 127.2, 127.3, 128.5, 128.8, 130.8, 139.9, 168.4$ ppm. IR (KBr): $\tilde{\nu} = 1678\text{ cm}^{-1}$. $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2$: C 70.80, H 8.37, N 9.75; found C 70.84, H 8.44, N 9.68. Exact mass calculated for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_2$: 288.3845; found 288.3852.

Preparation of Piperidone 16^[22]

(3R,3aS,6R,7aR)-1,1,3,6-Tetramethyl-4-oxo-5-((1S)-1-phenylethyl)-octahydroisoxazolo[4,3-c]pyridin-1-ium Trifluoromethanesulfonate (15): This was prepared from compound **13d** (0.5 mmol): 226 mg, 100% yield; sticky oil. ^1H NMR ($\text{CDCl}_3/\text{CD}_3\text{OD}$, 300 MHz): $\delta = 1.45$ (d, $J = 6.8$ Hz, 3 H), 1.65 (d, $J = 7.4$ Hz, 3 H), 1.75 (d, $J = 5.1$ Hz, 3 H), 2.47 (m, 2 H), 2.58 (m, 1 H), 3.35 (s, 3 H, $N\text{-CH}_3$), 3.65 (m, 2 H), 3.72 (s, 3 H, $N\text{-CH}_3$), 4.83 (dq, $J = 5.1, 7.3$ Hz, 1 H, H^3), 5.15 (m, 1 H, H^{7a}), 5.95 (q, $J = 7.4$ Hz, 1 H, $H^{5'}$), 7.52 (m, 5 H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 16.9, 17.0, 20.0, 20.1, 20.6, 29.5, 50.6, 52.0, 73.7, 82.8, 121.31$ (q, $J = 311.2$ Hz), 127.0, 127.2, 128.3, 129.0, 139.3, 168.3 ppm.

(3S,4R,6R)-4-(Dimethylamino)-3-((1R)-1-hydroxyethyl)-6-methyl-1-((1S)-1-phenylethyl)piperidin-2-one (16): 137 mg, 90% yield; colourless oil, $[\alpha]_{\text{D}}^{25} = -48.79$ ($c = 1.10$; CHCl_3). ^1H NMR ($\text{CDCl}_3/\text{CD}_3\text{OD}$, 300 MHz): $\delta = 1.35$ (d, $J = 6.9$ Hz, 3 H), 1.51 (d, $J = 5.7$ Hz, 3 H), 1.59 (d, $J = 7.1$ Hz, 3 H), 1.61 (dddd, $J = 6.8, 7.5, 14.1$ Hz, 1 H, H^{5a}), 2.05 (ddd, $J = 7.1, 8.3, 14.1$ Hz, 1 H, H^{5b}), 2.63 (s, 6 H, $N\text{-CH}_3$), 3.93 (dd, $J = 6.3, 7.5$ Hz, 1 H, H^3), 3.75 (ddd, $J = 6.9, 7.1, 7.5$ Hz, 1 H, H^6), 4.21 (ddd, $J = 6.3, 6.8, 8.3$ Hz, 1 H, H^4), 4.35 (dq, 1 H, $J = 5.7, 7.5$ Hz, $H^{3'}$), 5.85 (q, 1 H, $J = 7.1$ Hz, $H^{1'}$), 7.32 (m, 5 H) ppm. ^{13}C NMR (CDCl_3 , 75 MHz): $\delta = 19.5, 20.8, 21.7, 38.9, 39.3, 42.9, 47.6, 51.8, 52.9, 62.0, 128.2, 128.2, 128.30, 128.31, 126.5, 137.0, 175.9$ ppm. IR (KBr): $\tilde{\nu} = 1670\text{ cm}^{-1}$. $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_2$: C 71.02, H 9.27, N 9.20; found C 70.83, H 9.25, N 9.21. Exact mass calculated for $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}_2$: 304.2151; found 304.2152.

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