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Intramolecular cycloadditions of nitrones derived from optically active 1-alkenyl-2-imidazolecarbaldehydes: regio- and diastereoselectivity

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Abstract—Enantiopure polyfunctionalized imidazo[1,2-*a*]pyridines and pyrrolo[1,2-*a*]imidazoles, two classes of heterocyclic compounds including anti-inflammatories and glycosidase inhibitors, were synthesized starting from natural α-aminoacids and exploiting an intramolecular nitrone cycloaddition as the key step. The regiochemistry of the cycloaddition, which determines the product distribution, was markedly dependent on the R substituent and, therefore, submitted to a theoretical study by means of ab initio and MP2 calculations.

1. Introduction

Since the pioneering works of LeBel[1] and Oppolzer,[2] intramolecular nitrone cycloadditions have undergone an impressive diffusion as a general and efficient methodology for the synthesis of a wide variety of cyclic and open-chain structures, including complex natural substances and related unnatural compounds, for example, alkaloids, aminosugars and antibiotics.[3] The leading features of such methodology rely upon (i) the intrinsic peculiarities of the intramolecular cycloaddition process, particularly in terms of regiochemical and stereochemical constraints, and (ii) the easy and multiform manipulation of the primary isoxazolidine cycloadducts.

Our previous contributions in this field are concerned with nitrones already containing a heterocyclic skeleton, whose intramolecular cycloaddition may in principle constitute the key step for the construction of multi-ring heterocyclic structures related to natural compounds endowed with biological activities, namely pyrrolizidines, indolizidines, and indole alkaloids.[4] More recently, we have turned our attention to imidazo[1,2-*a*]pyridines, a class of compounds whose known syntheses suffer from a rather limited applicability[5] although some representatives have been proven active as anti-inflammatories and glycosidase inhibitors.[6] However, by using nitrones derived from 1-allyl-2-imidazolecarbaldehyde and chiral hydroxylamines, we have observed cycloaddition processes with a moderate degree of diastereoselectivity.[7] Herein, we report the behaviour of chiral nitrones, namely **6**, which possess a stereocentre within the tether joining the two reactive groups, so that a greater diastereofacial discrimination could have expected.

2. Results and discussion

As precursors of nitrones **6**, we conceived the chiral 1-(1-alkyl-allyl)-2-imidazolecarbaldehydes (*S*)-**5a** and **b**, which were accessible upon construction of the imidazole ring by the Gridnev method,[8] that is, by cyclocondensation between glyoxal, ammonium chloride, formaldehyde and the optically active allylamine phosphates (*S*)-**2a** and **b** (Scheme 1). The latter were in turn generated in situ upon acidic cleavage of the corresponding *N*-Boc protected amines (*S*)-**1a** and **b**, which we had prepared starting from L-alanine and L-valine methyl esters, respectively, as described in the literature.[9] The so-formed 1-(1-alkyl-allyl)-imidazoles (*S*)-**3a** and **b** were then subjected to 2-hydroxymethylation

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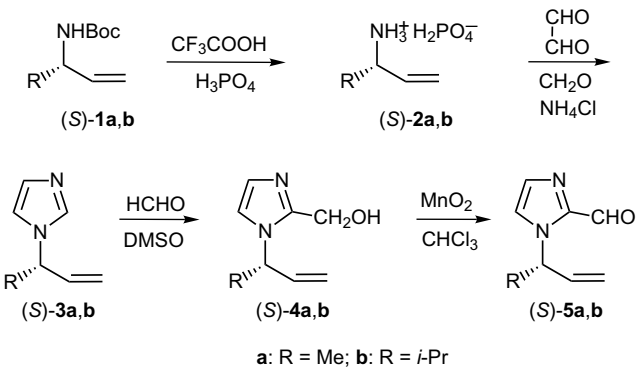
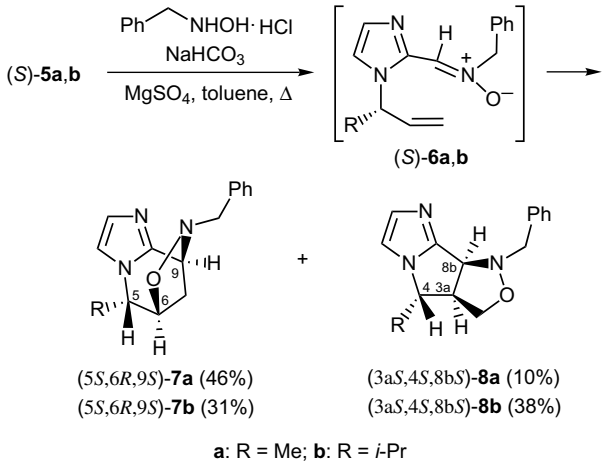


Scheme 1. Preparation of (*S*)-1-(1-alkyl-allyl)-2-imidazolecarbaldehydes.

and subsequent oxidation of the alcoholic function, this sequence being more convenient in comparison to the direct formylation of the imidazole nucleus.

With the aim of obtaining the desired nitrones, aldehydes (*S*)-**5a** and **b** were reacted with the commercial *N*-benzylhydroxylamine in refluxing toluene (Scheme 2). Actually, compounds (*S*)-**6a** and **b** were never isolated because they cyclized directly to produce the regioisomeric bridged-ring **7a** and **b** and fused-ring **8a** and **b** isoxazolidines. In both cases, the cycloaddition process led exclusively to a *cis*-junction of the new rings, clearly due to stringent geometric constraints. The relative configuration of the two new stereocentres with respect to the preexisting one was consistent with 1D NOESY experiments performed for the bridged structure **7a**, while for compound **8a** the 3% NOE effect between the methyl group in 4 position and H-3a revealed an *anti* relationship. Interestingly, as previously reported for encumbered isoxazolidines,[10] compounds **7a** and **b** suffer from restricted inversion at the pyramidal nitrogen so that they exist at room temperature as a 3:1 mixture of invertomers having different NMR signals. Of course, coalescence is observed at higher temperature.



Scheme 2. Reaction of (*S*)-1-(1-alkyl-allyl)-2-imidazolecarbaldehydes **5a**,**b** with *N*-benzylhydroxylamine.

The regiochemical outcome of the cycloaddition, markedly dependent on the substituent R, constitutes a striking feature and deserves explanation. To this end, a theoretical study was carried out by means of ab initio and MP2 calculations.

1,3-Dipolar cycloadditions of glyoxylic nitrones with electron-poor and electron-rich alkenes have been successfully modelled by Merino et al. by B3LYP/6-31G* DFT calculations.[11] Silva and Goodman were able to quantify the steric and electronic effect of various substituents on the dipolarophile by B3LYP/6-31G*//HF/6-31G* calculations, thus predicting the regiochemistry of some nitrone cycloadditions.[12] We decided to perform a range of calculations on the reactants **6**, the observed products **7** and **8**, and the transition states (TS) leading to them. Starting geometries for **6a** and **b**, **7a** and **b** and **8a** and **b** were located by a conformational search preformed with Hyperchem 6.3 at the AM1 level.[13] Transition structures **TS-7a** and **b** and **TS-8a** and **b** were located using the eigenvector-following method at the same level of theory.[14] All structures were then optimized ab initio at the RHF/6-31G** level. The computed transition structures are shown in Figure 1. The lengths of the C–C and C–O forming bonds, which are in good agreement with those computed by Merino at the B3LYP/6-31G* level, indicate a synchronous concerted mechanism for cycloadducts **7**, while correspond to a certain degree of asynchronicity in the formation of **8**. The electron correlation effect was evaluated by MP2/6-31+G** single point calculations on the HF optimized structures. In order to state in which measure our calculated energies were basis set dependent, we recalculated the MP2 energies using the triple split-valence 6-311ł+G** basis set,[15] obtaining similar results. MP2 energy values are reported in Table 1. One can see that the predicted energies by MP2 single point calculations fit well to the observed regiochemical outcome. In the case **a** (R = Me), the calculated activation energy is about 2.3 kcal/mol lower for **TS-7a** and the bridged-ring cycloadduct **7a** results almost 7 kcal/mol more stable than **8a**. Conversely, in the case **b** (R = *i*-Pr), the potential energy barrier is about 1.5 kcal/mol lower for **TS-8b**, although the product **7b** remains more stable than **8b** of about 4.5 kcal/mol. This indicates that the formation of cycloadduct **7a** is favoured over **8a** on both kinetic and thermodynamic grounds. Instead, in the case of the more encumbered nitrone **6b**, a closer competition between the two possible regioisomers **7b** and **8b** comes out from the theoretical data, in accord with the modest degree of observed regioselectivity. It has to be added that the HF energy values did not correctly describe the regiochemical outcome of the considered reactions, as the condensed TS were predicted more stable in both cases **a** and **b**. By the introduction of the electronic correlation, MP2 single point calculations were able to predict the formation of **7a** as the major product. Such method dependence in predicting nitrone cycloadditions has been observed also by Merino et al., who treated the electron correlation effect by DFT methods.[11b] The full diastereoselectivity of the cycloaddition, within the experimental error limits, can plausibly be explained for on the basis of the following assumptions: (i) the *Z*-form of the nitrone group is more suitable to the

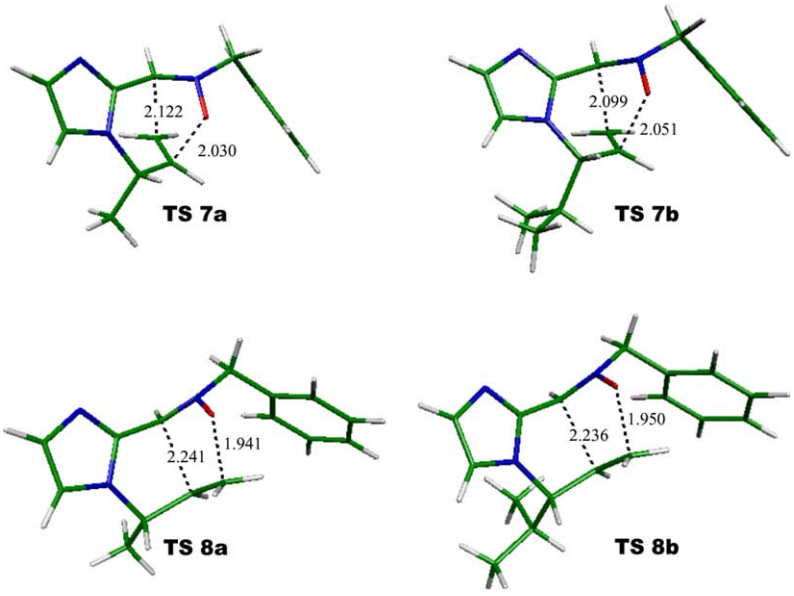


Figure 1. Computed structures for transition states leading to the cycloadducts **7a** and **b** and **8a** and **b**. Predicted lengths of C–C and C–O forming bonds are reported in angstroms.[16]

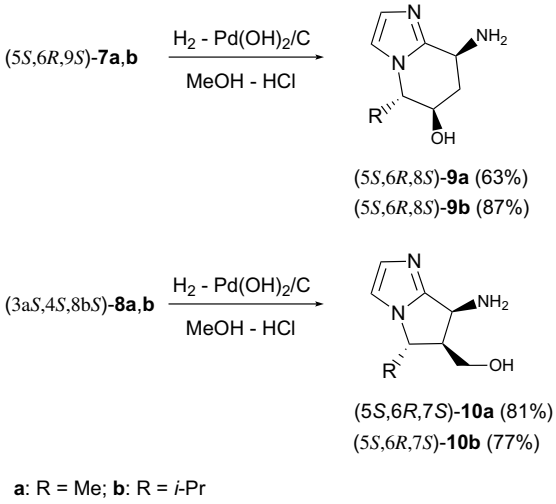
Table 1. Total electronic energies E_{tot} and relative energies E_{rel}[a]

Structure	E_{tot} [a.u.]	E_{rel} [kcal/mol]
6a	−819.075188 (−818.749242)	0
TS-7a	−819.057771 (−818.731176)	10.9 (11.3)
TS-8a	−819.054132 (−818.727466)	13.2 (13.7)
7a	−819.115884 (−818.791873)	−25.5 (−26.8)
8a	−819.105114 (−818.780772)	−18.8 (−19.8)
6b	−897.475833 (−897.120913)	0
TS-7b	−897.450954 (−897.095360)	15.6 (16.0)
TS-8b	−897.453622 (−897.097639)	13.9 (14.6)
7b	−897.508893 (−897.155965)	−20.7 (−22.0)
8b	−897.502010 (−897.148432)	−16.5 (−17.3)

[a] By MP2/6-311++G** (in parentheses by MP2/6-31+G**).

intramolecular reaction than the *E*-form; (ii) when the two planes containing the reactive groups are approaching each other, the R substituent remains outside in order to minimize the steric repulsions. This means that, as just depicted in Figure 1, the *Z*-nitrone is forced to attack the *si* face of the dipolarophile for the fused-ring mode and the *re* one in the bridged-ring mode.

The last step of our synthetic plan was the catalytic hydrogenation of compounds **7a** and **b** and **8a** and **b** in order to achieve functionalized bicyclic products coming from cleavage of the N–O bond and loss of the benzylic group. Disappointing results were obtained when using common catalysts (Pd/C, $Pd(OH)_2$, PtO_2) in pure methanol. In contrast, a satisfactory reaction occurred in acidic medium, namely by dissolving the organic substrates in a 2 M solution of HCl in methanol. Under these conditions, as depicted in Scheme 3, the imidazo[1,2-*a*]pyridines (−)-**9a** and **b** and pyrrolo[1,2-*a*]imidazoles (+)-**10a** and **b** were isolated in good yields after treatment of the reaction mixture with 50% aqueous NaOH.



Scheme 3. Hydrogenation of the cycloadducts **7a** and **b** and **8a** and **b**.

In the case of aminoalcohols **9a** and **10a**, the enantiomeric purity was proven by recording their NMR spectrum in the presence of (*R*)-*O*-acetylmandelic acid and comparing it with that of the corresponding racemate. The latter materials were available on submitting the racemic 2-methylallylamine[17] to the reaction sequence described for (*S*)-**2a**.

3. Experimental section

3.1. General

Melting points were determined on a Büchi B-540 heating apparatus and are uncorrected. IR spectra were recorded on a FT-IR Perkin–Elmer 1725X

spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on an AVANCE Bruker 400. Chemical shifts are given in ppm downfield from $SiMe_4$. Mass spectra were determined on a WG-70EQ instrument. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Column chromatographies were performed on Merck Kieselgel 60, 0.063–0.2 mm.

3.2. General procedure for the preparation of (*S*)-1-(1-alkyl-allyl)-1*H*-imidazoles 3a and b

A solution of (*S*)-**1** (19.6 mmol) in CF_3COOH (1.49 mL, 19.6 mmol) was stirred at 0 °C for 30 min under N_2. After addition of 85% H_3PO_4 (4.02 mL, 58.8 mmol), H_2O (10 mL), 40% glyoxal (2.24 mL, 19.6 mmol) and 37% formaldehyde (1.49 mL, 19.6 mmol), 0.98 M aqueous NH_4Cl (20 mL, 19.6 mmol) was dropped during 1.5 h under stirring at 95 °C. After 30 min the mixture was cooled to room temperature, adjusted to pH 8 with solid KOH and extracted with AcOEt (5 × 50 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude residue so obtained was chromatographed on a silica gel column with $CHCl_3$/EtOH 20:1 as eluent to give **3a** and **b**.

3.2.1. (*S*)-1-(1-Methyl-allyl)-1*H*-imidazole 3a. Yield: 39%. Oil. $[\alpha]_D^{23} = +25.9$ (*c* 0.14, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.58 (3H, d, $J = 6.9$ Hz), 4.73 (1H, dq, $J = 5.7$, 6.9 Hz), 5.09 (1H, d, $J = 17.1$ Hz), 5.20 (1H, d, $J = 10.4$ Hz), 5.95 (1H, ddd, $J = 5.7$, 10.4, 17.1 Hz), 6.92 (1H, s), 7.05 (1H, s), 7.52 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.0 (q), 55.3 (d), 116.7 (t), 117.7 (d), 129.4 (d), 136.0 (d), 138.6 (d). MS: *m*/*z* 122 (M^+). Anal. Calcd for $C_7H_{10}N_2$: C, 68.82; H, 8.25; N, 22.93. Found C, 68.99; H, 8.08; N, 23.02.

3.2.2. (*S*)-1-(1-Isopropyl-allyl)-1*H*-imidazole 3b. Yield: 37%. Oil. $[\alpha]_D^{23} = +48.8$ (*c* 0.84, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 0.81 (3H, d, $J = 6.7$ Hz), 0.99 (3H, d, $J = 6.7$ Hz), 2.09 (1H, dqq, $J = 6.7$, 6.7, 8.0 Hz), 4.17 (1H, dd, $J = 8.0$, 8.0 Hz), 5.17 (1H, d, $J = 17.0$ Hz), 5.28 (1H, d, $J = 10.3$ Hz), 6.02 (1H, ddd, $J = 8.0$, 10.3, 17.0 Hz), 6.95 (1H, s), 7.11 (1H, s), 7.54 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) 19.4 (q), 19.6 (q), 33.3 (d), 67.6 (d), 115.9 (d), 119.1 (t), 130.0 (d), 135.7 (d), 135.8 (d). MS: *m*/*z* 150 (M^+). Anal. Calcd for $C_9H_{14}N_2$: C, 71.96; H, 9.39; N, 18.65. Found C, 72.01; H, 9.53; N, 18.45.

3.3. General procedure for the preparation of (*S*)-[1-(1-alkyl-allyl)-1*H*-imidazol-2-yl]-methanol derivatives 4a and b

A solution of (*S*)-3 (4.8 mmol), 37% formaldehyde (1.46 mL, 19.6 mmol) and AcOH (0.5 mL) in DMSO (30 mL) was stirred for 60 h at 130 °C. After cooling to room temperature, H_2O (70 mL) was added. The solution was adjusted to pH 9 with 32% aqueous ammonia and extracted with AcOEt (5 × 50 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was chromatographed on a silica gel column with $CHCl_3$/EtOH 9:1 as eluent to give **4a** and **b**.

3.3.1. (*S*)-[1-(1-Methyl-allyl)-1*H*-imidazol-2-yl]-methanol 4a. Yield: 66%. Oil. $[\alpha]_D^{23} = -24.7$ (*c* 0.92, $CHCl_3$). IR (nujol): 3400 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.54 (3H, d, $J = 6.8$ Hz), 4.61, 4.67 (2H, AB system, $J = 13.7$ Hz), 5.03 (1H, d, $J = 17.1$ Hz), 5.01 (1H, dq, $J = 5.8$, 6.8 Hz), 5.17 (1H, d, $J = 10.2$ Hz), 5.24 (1H, br s, missing after deuteriation), 5.77 (1H, ddd, $J = 5.8$, 10.2, 17.1 Hz), 6.85 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.0 (q), 53.4 (d), 56.4 (t), 116.2 (t), 117.4 (d), 127.2 (d), 138.7 (d), 147.7 (s). MS: *m*/*z* 152 (M^+). Anal. Calcd for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found C, 63.05; H, 8.03; N, 18.58.

3.3.2. (*S*)-[1-(1-Isopropyl-allyl)-1*H*-imidazol-2-yl]-methanol 4b. Yield: 56%. Mp 65–67 °C (diisopropyl ether). $[\alpha]_D^{23} = +27.8$ (*c* 2.4, $CHCl_3$). IR (nujol): 3447 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.80 (3H, d, $J = 6.6$ Hz), 1.04 (3H, d, $J = 6.6$ Hz), 2.05 (1H, dqq, $J = 6.6$, 6.6, 7.6 Hz), 4.50 (1H, dd, $J = 7.4$, 7.6 Hz), 4.62, 4.68 (2H, AB system, $J = 13.7$ Hz), 5.12 (1H, d, $J = 17.0$ Hz), 5.21 (1H, d, $J = 10.3$ Hz), 5.81 (1H, br s, missing after deuteriation), 5.96 (1H, ddd, $J = 7.4$, 10.3, 17.0 Hz), 6.83 (1H, s), 6.84 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7 (q), 20.1 (q), 33.4 (d), 56.4 (t), 65.3 (d), 117.2 (d), 118.5 (t), 127.1 (d), 136.5 (d), 148.2 (s). MS: *m*/*z* 180 (M^+). Anal. Calcd for $C_{10}H_{16}N_2O$: C, 66.64; H, 8.95; N, 15.54. Found C, 66.54; H, 9.14; N, 15.39.

3.4. General procedure for the preparation of (*S*)-1-(1-alkyl-allyl)-1*H*-imidazole-2-carbaldehydes 5a and b

A suspension of (*S*)-4 (0.54 mmol) and activated MnO_2 (340 mg, 3.9 mmol) in $CHCl_3$ (7 mL) was stirred for 24 h at 60 °C. After cooling and filtration on a Celite path, the solvent was removed under reduced pressure to give **5a** and **b** in pure state.

3.4.1. (*S*)-1-(1-Methyl-allyl)-1*H*-imidazole-2-carbaldehyde 5a. Yield: 89%. Oil. $[\alpha]_D^{23} = -16.9$ (*c* 0.58, $CHCl_3$). IR (nujol): 1688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 1.56 (3H, d, $J = 6.7$ Hz), 5.06 (1H, d, $J = 15.7$ Hz), 5.24 (1H, d, $J = 9.1$ Hz), 5.95–6.06 (2H, overlapping), 7.27 (1H, s), 7.30 (1H, s), 9.83 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.9 (q), 54.3 (d), 117.1 (t), 123.3 (d), 132.3 (d), 137.8 (d), 143.4 (s), 182.7 (d). MS: *m*/*z* 150 (M^+). Anal. Calcd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found C, 63.95; H, 6.53; N, 18.72.

3.4.2. (*S*)-1-(1-Isopropyl-allyl)-1*H*-imidazole-2-carbaldehyde 5b. Yield: 83%. Oil. $[\alpha]_D^{23} = +19.74$ (*c* 0.98, $CHCl_3$). IR (nujol): 1694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.67 (3H, d, $J = 6.7$ Hz), 0.89 (3H, d, $J = 6.7$ Hz), 1.98 (1H, dqq, $J = 6.7$, 6.7, 9.1 Hz), 5.12 (1H, d, $J = 17.4$ Hz), 5.17 (1H, d, $J = 10.3$ Hz), 5.48 (1H, dd, $J = 8.6$, 9.1 Hz), 5.90 (1H, ddd, $J = 8.6$, 10.3, 17.4 Hz), 7.21 (1H, s), 7.23 (1H, s), 9.73 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.4 (q), 19.5 (q), 33.6 (d), 65.4 (d), 119.8 (t), 123.7 (d), 132.3 (d), 135.5 (d), 143.8 (s), 182.8 (d). MS: *m*/*z* 178 (M^+). Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found C, 67.21; H, 8.03; N, 15.79.

3.5. General procedure for the reactions of 5a and b with *N*-benzylhydroxylamine

A suspension of *N*-benzylhydroxylamine hydrochloride (1.3 g, 8.2 mmol), $NaHCO_3$ (2.0 g, 23 mmol) and $MgSO_4$ (16.0 g, 130 mmol) in dry toluene (150 mL) was stirred for 10 min, then a solution of **5a** and **b** (6.7 mmol) in toluene (10 mL) was added. The mixture was stirred for 24 h at reflux, filtered and evaporated. The remaining slurry was chromatographed on a silica gel column with the eluent given below.

Entry **a**: elution with AcOEt/light petroleum/EtOH (7:2:1) gave **8a** (10%) and **7a** (46%).

3.5.1. (3a*S*,4*S*,8b*S*)-1-Benzyl-4-methyl-1,3a,4,8b-tetrahydro-3*H*-imidazo[1′,2′:1,2]pyrrolo[3,4-*c*]isoxazole 8a. Oil. $[\alpha]_D^{23} = +10.7$ (*c* 0.23, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 55 °C) δ: 1.48 (3H, d, $J = 6.5$ Hz), 3.54 (1H, dddd, $J = 3.3$, 3.5, 7.6, 10.8 Hz), 3.92 (1H, dd, $J = 3.3$, 9.0 Hz), 4.12–4.31 (3H, overlapping), 4.29 (1H, dq, $J = 3.5$, 6.5 Hz), 4.56 (1H, d, $J = 7.6$ Hz), 6.85 (1H, s), 7.19 (1H, s), 7.24–7.47 (5H, overlapping); ^{13}C NMR (100 MHz, $CDCl_3$) 22.8 (q), 30.1 (t), 31.6 (d), 58.5 (d), 59.4 (d), 59.6 (t), 113.7 (d), 127.8 (d), 128.7 (d), 129.4 (d), 135.1 (d), 138.7 (s), 152.1 (s). MS: *m*/*z* 255 (M^+). Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found C, 70.61; H, 6.53; N, 16.26.

3.5.2. (5*S*,6*R*,9*S*)-8-Benzyl-5-methyl-5,6,8,9-tetrahydro-6,9-methanoimidazo[2,1-*d*][1,2,5]oxadiazepine 7a. Oil. $[\alpha]_D^{23} = -7.4$ (*c* 0.64, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, *major invertomer*) δ: 1.27 (3H, br s), 2.29 (1H, br s), 2.85 (1H, br s), 3.30 (1H, br s), 3.84 (1H, br s), 4.11 (1H, br s), 4.49 (1H, br s), 4.55 (1H, br s), 7.00 (1H, br s), 7.10 (1H, br s), 7.17–7.46 (5H, overlapping); ^1H NMR (400 MHz, $CDCl_3$, *minor invertomer*) δ: 1.27 (3H, br s), 2.02 (1H, br s), 2.75 (1H, br s), 3.65 (1H, br s), 3.74–4.68 (3H, overlapping), 5.35 (1H, br s), 6.86 (1H, br s), 7.18 (1H, br s), 7.17–7.46 (5H, overlapping); ^1H NMR (400 MHz, DMSO, 100 °C): 1.42 (3H, d, $J = 6.7$ Hz), 2.26 (1H, d, $J = 11.6$ Hz), 2.70 (1H, ddd, $J = 4.6$, 6.2, 11.6 Hz), 3.84, 3.64 (2H, AB system, $J = 13.6$ Hz), 4.12 (1H, dq, $J = 1.6$, 6.7 Hz), 4.37 (1H, d, $J = 4.6$ Hz), 4.61 (1H, dd, $J = 1.6$, 6.2 Hz), 6.85 (1H, br s), 7.11 (1H, br s), 7.23–7.43 (5H, overlapping); ^{13}C NMR (100 MHz, $CDCl_3$, *major invertomer*) δ: 18.4 (q), 36.8 (t), 57.2 (d), 57.4 (d), 59.6 (t), 76.5 (d), 117.4 (d), 127.8 (d), 128.8 (d), 129.5 (d), 130.2 (d), 137.6 (s), 145.0 (s); ^{13}C NMR (100 MHz, $CDCl_3$, *minor invertomer*) 18.4 (q), 36.8 (t), 53.0 (d), 53.9 (d), 59.6 (t), 76.9 (d), 117.0 (d), 127.8 (d), 128.8 (d), 129.5 (d), 130.2 (d), 137.6 (s), 145.0 (s). MS: *m*/*z* 255 (M^+). Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found C, 70.39; H, 6.74; N, 16.52.

Entry **b**: elution with AcOEt gave **8b** (38%) and **7b** (31%).

3.5.3. (3a*S*,4*S*,8b*S*)-1-Benzyl-4-isopropyl-1,3a,4,8b-tetrahydro-3*H*-imidazo[1′,2′:1,2]pyrrolo[3,4-*c*]isoxazole 8b. Oil. $[\alpha]_D^{23} = +6.7$ (*c* 0.804, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 55 °C): 0.80 (3H, d, $J = 6.8$ Hz), 0.94 (3H, d, $J = 6.8$ Hz), 2.11 (1H, dqq, $J = 6.8$, 6.8, 8.9 Hz), 3.55–3.64 (1H, m), 3.84 (1H, dd, $J = 3.6$, 8.9 Hz), 4.10 (1H, dd, $J = 3.3$, 3.6 Hz), 4.12–4.29 (3H, overlapping), 4.53 (1H, d, $J = 7.8$ Hz), 6.87 (1H, s), 7.19 (1H, s), 7.26 (1H, d, $J = 7.2$ Hz), 7.32 (2H, dd, $J = 7.2$, 7.5 Hz), 7.46 (2H, d, $J = 7.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 17.2 (q), 18.2 (q), 32.9 (d), 48.3 (t), 52.8 (d), 53.0 (d), 61.0 (t), 68.4 (d), 114.8 (d), 127.8 (d), 128.5 (d), 129.4 (d), 134.2 (d), 137.5 (s), 150.8 (s). MS: *m*/*z* 283 (M^+). Anal. Calcd for $C_{17}H_{21}N_3O$: C, 72.06; H, 7.47; N, 14.83. Found C, 71.97; H, 7.51; N, 14.72.

3.5.4. (5*S*,6*R*,9*S*)-8-Benzyl-5-isopropyl-5,6,8,9-tetrahydro-6,9-methanoimidazo[2,1-*d*][1,2,5]oxadiazepine 7b. Oil. $[\alpha]_D^{23} = +24.2$ (*c* 0.48, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, *major invertomer*) δ: 0.92 (3H, d, $J = 6.9$ Hz), 1.15 (3H, d, $J = 6.9$ Hz), 2.19 (1H, dqq, $J = 5.6$, 6.9, 6.9 Hz), 2.44 (1H, br s), 3.68–3.74 (2H, overlapping), 3.75–4.11 (2H, overlapping), 4.52 (1H, d, $J = 4.3$ Hz); 4.74 (1H, br s), 7.03 (1H, br s), 7.09 (1H, br s), 7.19–7.39 (5H, overlapping); ^1H NMR (400 MHz, $CDCl_3$, *minor invertomer*) δ: 0.92 (3H, d, $J = 6.9$ Hz), 1.15 (3H, d, $J = 6.9$ Hz), 2.19 (1H, dqq, $J = 5.6$, 6.9, 6.9 Hz), 2.36 (1H, br s), 2.62 (1H, br s), 3.15 (1H, br s), 3.75–4.11 (2H, overlapping), 4.52 (1H, d, $J = 4.3$ Hz), 4.88 (1H, br s), 7.03 (1H, br s), 7.09 (1H, br s), 7.19–7.39 (5H, overlapping); ^1H NMR (400 MHz, DMSO, 120 °C): 0.92 (3H, d, $J = 6.9$ Hz), 1.09 (3H, d, $J = 6.9$ Hz), 2.20 (1H, dqq, $J = 5.6$, 6.9, 6.9 Hz), 2.36 (1H, d, $J = 11.9$ Hz), 2.65 (1H, ddd, $J = 4.4$, 6.2, 11.9 Hz), 3.61, 3.81 (2H, AB system, $J = 13.6$ Hz), 3.89 (1H, dd, $J = 1.9$, 5.6 Hz), 4.38 (1H, d, $J = 4.4$ Hz), 4.82 (1H, dd, $J = 1.9$, 6.2 Hz), 6.87 (1H, d, $J = 1.3$ Hz), 7.11 (1H, d, $J = 1.3$ Hz), 7.23–7.38 (5H, overlapping); ^{13}C NMR (100 MHz, $CDCl_3$, *major invertomer*) δ: 19.0 (q), 20.6 (q), 31.3 (d), 34.7 (t), 58.0 (d), 59.8 (t), 68.0 (d), 74.3 (d), 118.8 (d), 127.7 (d), 128.4 (d), 128.8 (d), 129.3 (d), 137.7 (s), 145.3 (s). ^{13}C NMR (100 MHz, $CDCl_3$, *minor invertomer*) 19.0 (q), 20.6 (q), 31.3 (d), 34.7 (t), 58.4 (d), 63.6 (t), 69.6 (d), 74.8 (d), 117.7 (d), 127.8 (d), 128.4 (d), 128.8 (d), 129.3 (d), 137.4 (s), 145.3 (s). MS: *m*/*z* 283 (M^+). Anal. Calcd for $C_{17}H_{21}N_3O$: C, 72.06; H, 7.47; N, 14.83. Found C, 72.06; H, 7.33; N, 14.88.

3.6. General procedure for the hydrogenation of compounds 7a and b and 8a and b

A suspension of 20% $Pd(OH)_2/C$ (53 mg, 0.078 mmol) and isoxazolidinic compound (0.039 mmol) in a 0.09 M HCl solution in MeOH (10 mL) was stirred under H_2 for 24 h. After filtration through Celite, the solvent was removed under reduced pressure to give 1,3-aminoalcohol hydrochloride as a white solid. The latter was treated with H_2O (2 mL) and KOH (75 mg, 1.34 mmol) and extracted with $CHCl_3$ (5×50 mL). The organic solution was dried over Na_2SO_4 and evaporated under reduced pressure to give 1,3-aminoalcohol.

3.6.1. (5*S*,6*R*,8*S*)-8-Amino-5-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridin-6-ol 9a. Yield: 63%. Oil. $[\alpha]_D^{23} = -15.2$ (*c* 0.09, $CHCl_3$). IR (nujol): 3684, 3619,

3455 cm^{-1}; ^{1}H NMR of hydrochloride compound (400 MHz, D_2O) δ: 1.40 (3H, d, J = 7.0 Hz), 2.42 (1H, ddd, J = 2.8, 5.1, 14.3 Hz), 2.49 (1H, ddd, J = 2.0, 5.8, 14.3 Hz), 4.36 (1H, ddd, J = 2.0, 2.4, 5.1 Hz), 4.60 (1H, dq, J = 2.4, 7.0 Hz), 4.99 (1H, dd, J = 2.8, 5.8 Hz), 7.53, 7.58 (2H, AB system, J = 2.1 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.63 (3H, d, J = 6.6 Hz), 2.01 (1H, ddd, J = 2.1, 4.3, 14.3 Hz), 2.31 (1H, ddd, J = 2.3, 4.5, 14.3 Hz), 2.95 (3H, br s, missing after deuteriation), 3.99 (1H, dq, J = 2.8, 6.6 Hz), 4.15 (1H, ddd, J = 2.3, 2.8, 4.3 Hz), 4.55 (1H, dd, J = 2.1, 4.3 Hz), 6.95 (1H, s), 7.07 (1H, s); ^{13}C NMR of hydrochloride compound (100 MHz, D_2O) δ: 18.9 (q), 26.2 (t), 40.5 (d), 60.0 (d), 66.9 (d), 121.9 (d), 122.4 (d), 136.8 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.4 (q), 33.6 (t), 44.6 (d), 56.3 (d), 69.0 (d), 117.1 (d), 128.9 (d), 145.9 (s). MS: m/z 167 (M^+). Anal. Calcd for $C_8H_{13}N_3O$: C, 57.47; H, 7.84; N, 25.13. Found C, 57.30; H, 7.73; N, 24.99.

3.6.2. (5*S*,6*R*,7*S*)-(7-Amino-5-methyl-6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-6-yl)-methanol 10a. Yield: 81%. Oil. $[\alpha]_D^{23} = +15.74$ (c 0.21, $CHCl_3$). IR (nujol): 3684, 3619, 3389 cm^{-1}; ^{1}H NMR of hydrochloride compound (400 MHz, D_2O) δ: 1.57 (3H, d, J = 6.5 Hz), 3.20 (1H, dddd, J = 3.9, 3.9, 5.8, 7.9 Hz), 3.94 (1H, dd, J = 5.8, 12.6 Hz), 4.03 (1H, dd, J = 3.9, 12.6 Hz), 4.71 (1H, dq, J = 3.9, 6.5 Hz), 5.22 (1H, d, J = 7.9 Hz), 7.54, 7.58 (2H, AB system, J = 2.0); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.48 (3H, d, J = 6.4 Hz), 2.60 (1H, dddd, J = 3.4, 6.4, 6.5, 7.7 Hz), 2.78 (3H, br s, missing after deuteriation), 3.87 (1H, dd, J = 6.4, 11.9 Hz), 4.02 (1H, dd, J = 3.4, 11.9 Hz), 4.34 (1H, dq, J = 6.4, 6.5 Hz), 4.54 (1H, d, J = 7.7 Hz), 6.86 (1H, s), 7.10 (1H, s); ^{13}C NMR of hydrochloride compound (100 MHz, D_2O): 17.4 (q), 47.8 (d), 52.7 (d), 56.9 (t), 57.3 (d), 118.3 (d), 125.7 (d), 143.4 (s); ^{13}C NMR (100 MHz, $CDCl_3$): 20.3 (q), 49.6 (d), 53.2 (d), 55.4 (d), 60.9 (t), 113.6 (d), 133.9 (d), 155.1 (s). MS: m/z 167 (M^+). Anal. Calcd for $C_8H_{13}N_3O$: C, 57.47; H, 7.84; N, 25.13. Found C, 57.52; H, 7.98; N, 25.04.

3.6.3. (5*S*,6*R*,8*S*)-8-Amino-5-isopropyl-5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyridin-6-ol 9b. Yield: 87%. Mp 164–165 °C (diisopropyl ether). $[\alpha]_D^{23} = -11.4$ (c 0.21, $CHCl_3$). IR (nujol): 3665, 3600, 3416 cm^{-1}; ^{1}H NMR of hydrochloride compound (400 MHz, D_2O) δ: 0.84 (3H, d, J = 6.3 Hz), 0.91 (3H, d, J = 6.3 Hz), 1.93–1.95 (1H, m), 2.34 (1H, br d, J = 14.8 Hz), 2.49 (1H, br d, J = 14.8 Hz), 4.17 (1H, br d, J = 6.7 Hz), 4.58 (1H, br s), 4.89 (1H, br s), 7.39 (1H, s), 7.45 (1H, s); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.94 (3H, d, J = 6.8 Hz), 1.01 (3H, d, J = 6.8 Hz), 1.90 (1H, dqq, J = 6.8, 6.8, 6.8 Hz), 2.15 (2H, br s), 3.15 (3H, br s, missing after deuteriation), 4.02 (1H, br d, J = 6.8 Hz), 4.35 (1H, br s), 4.51 (1H, br s), 6.90 (1H, s), 7.07 (1H, s); ^{13}C NMR of hydrochloride compound (100 MHz, D_2O) δ: 18.3(q), 19.4 (q), 27.9 (t), 31.8 (d), 41.1 (d), 63.7(d), 68.7 (d), 123.1(d), 123.5 (d), 138.1 (s); ^{13}C NMR (100 MHz, $CDCl_3$): 19.8 (q), 20.6 (q), 31.7 (t), 32.9 (d), 44.3 (d), 66.9 (d), 68.7 (d), 120.1 (d), 128.5 (d), 145.7 (s). MS: 195 m/z (M^+). Anal. Calcd for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.78; N, 21.52. Found C, 61.44; H, 8.66; N, 21.50.

3.6.4. (5*S*,6*R*,7*S*)-(7-Amino-5-isopropyl-6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-6-yl)-methanol 10b. Yield: 77%. Oil. $[\alpha]_D^{23} = +10.3$ (c 0.30, $CHCl_3$). IR (nujol): 3688, 3619, 3391 cm^{-1}; ^{1}H NMR of hydrochloride compound (400 MHz, D_2O) δ: 0.77 (3H, d, J = 6.9 Hz), 0.88 (3H, d, J = 6.9 Hz), 2.27 (1H, dqq, J = 4.5, 6.9, 6.9 Hz), 3.38 (1H, dddd, J = 4.4, 4.5, 6.1, 8.6 Hz), 3.85 (1H, dd, J = 6.1, 12.4 Hz), 3.94 (1H, dd, J = 4.4, 12.4 Hz), 4.53 (1H, dd, J = 4.5, 4.5 Hz), 5.30 (1H, d, J = 8.6 Hz), 7.52 (1H, s), 7.54 (1H, s); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.84 (3H, d, J = 6.8 Hz), 0.93 (3H, d, J = 6.8 Hz), 2.07 (1H, dqq, J = 3.9, 6.8, 6.8 Hz), 2.48 (3H, br s, missing after deuteriation), 2.87 (1H, ddd, J = 3.9, 3.9, 7.7, 8.4 Hz), 3.77 (1H, dd, J = 7.7, 11.7 Hz), 3.94 (1H, dd, J = 3.9, 11.7 Hz), 3.92 (1H, dd, J = 3.9, 3.9 Hz), 4.55 (1H, d, J = 8.4 Hz), 6.83 (1H, s), 7.09 (1H, s); ^{13}C NMR of hydrochloride compound (100 MHz, D_2O) δ: 16.6 (q), 17.0 (q), 30.7 (d), 46.2 (d), 49.3 (d), 59.4 (t), 67.3 (d), 119.1(d), 126.1 (d), 144.1 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.8 (q), 18.1 (q), 32.6 (d), 49.0 (d), 49.5 (d), 63.3 (t), 64.1 (d), 119.9 (d), 134.9 (d), 142.6 (s). MS: 195 m/z (M^+). Anal. Calcd for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.78; N, 21.52. Found C, 61.61; H, 8.97; N, 21.41.

3.7. Computations

All ab initio calculations were performed with GAMESS on a HP Superdome machine running HP-UX.[18] In addition to that described in the general section, the following details must be given. The Hessian matrix was calculated numerically for all optimized structures to prove the location of correct minima (no imaginary frequency) or saddle points (only one negative eigenvalue corresponding to the formation of new bonds). For a better MP2 accuracy the linear dependence threshold was set at 1×10^{-7}, HONDO/Rys integrals were used for all integrals, the primitive and integrals cutoff factors were set, respectively, at 1×10^{-30} and 1×10^{-11}, and DIIS converger was used instead of SOSCF.

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