Pergamon

Tetrahedron 58 (2002) 4445–4450

TETRAHEDRON

Synthetic approach to imidazo[1,2-*a*]pyridine derivatives by the intramolecular nitrone cycloaddition methodology

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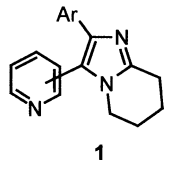
Received 16 January 2002; accepted 11 April 2002

Abstract—*N*-Benzyl and (*R*)-*N*-(α-phenylethyl) nitrones derived from 1-allyl-2-imidazolecarbaldehyde underwent intramolecular cycloaddition to give predominantly bridged-ring products, namely 5,6,8,9-tetrahydro-6,9-methanoimidazo[2,1-*d*][1,2,5]oxadiazepine derivatives. Catalytic hydrogenation of the latter furnished both racemic and enantiopure 6,8-functionalised 5,6,7,8-tetrahydro-imidazo[1,2-*a*]pyridines. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Imidazo[1,2-*a*]pyridine derivatives are attracting interest since some of them present pharmacological properties as antiinflammatories,[1] e.g. compounds of formula **1**, or as glycosidase inhibitors, which include the well-known nagstatin **2** and its debranched analogue **3**.[2] A number of molecules containing this bicyclic skeleton have been described, both partially and fully saturated. However, most of their syntheses seem rather occasional and suffer from limited applicability.[3] To our knowledge, the only synthetic approaches of general value to imidazo[1,2-*a*]pyridines are: (i) the cyclocondensation of ethylendiamines with 1,5-dicarbonyl compounds[4] and (ii) the cyclization of 1-(imidazolyl)substituted aldoses.[5]



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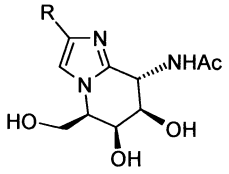


2 R = CH_2COOH
3 R = H

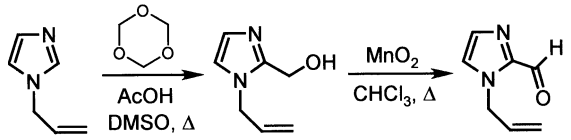
Intramolecular nitrone cycloadditions are known to constitute an important tool in order to build complex heteropolycyclic systems with a high degree of regio- and stereocontrol.[6] Due to the formation of a dihydroisoxazole or an isoxazolidinic ring, the resultant structures contain masked functionalities which can be brought to light under reductive[7] or oxidative[8] conditions. Consequently, this methodology has been successful for the preparation of a variety of natural and unnatural compounds with biological activities.[6,7]

On continuing our research dealing with intramolecular nitrone cycloaddition methodology as a route to alkaloid-like molecules,[9] we have investigated the accessibility of the imidazo[1,2-*a*]pyridine system by way of nitrones derived from 1-allyl-2-imidazolecarbaldehyde (**5**).

2. Results and discussion

First, we prepared the unknown aldehyde **5**, starting from the commercially available 1-allylimidazole through hydroxymethylation followed by oxidation (Scheme 1).

To convert **5** into a nitrone species, we chose benzylhydroxylamine due to: (i) its commercial availability, (ii) the easy removal of the benzyl residue, and (iii) the possibility of generating an optically active nitrone when



4 **5**

Scheme 1. Preparation of 1-allyl-2-imidazolecarbaldehyde.

Keywords: imidazo[1,2-*a*]pyridines; nitrones; intramolecular cycloaddition.

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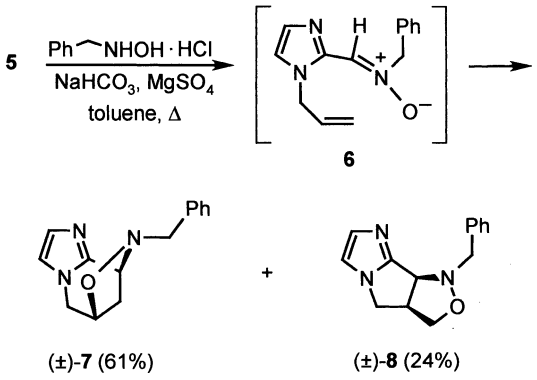
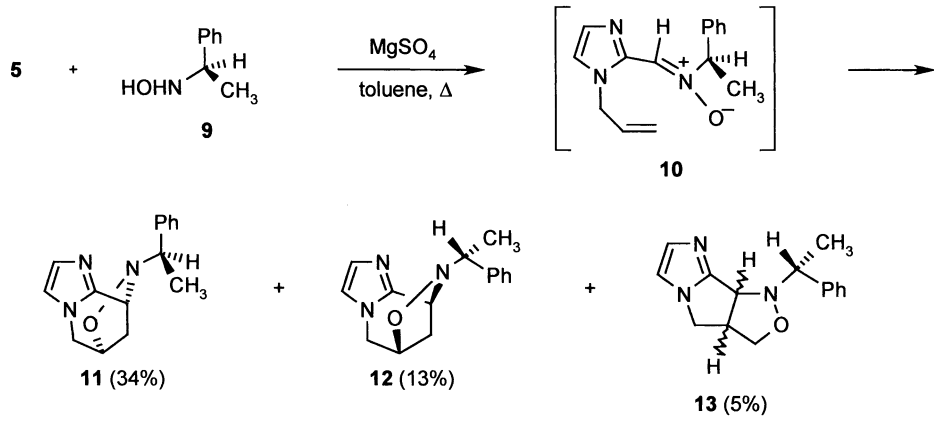
PII: S0040-4020(02)00404-0



Scheme 2. Intramolecular cycloaddition of nitrone **6**.

cycloadducts, we used (*R*)-α-phenylethylhydroxylamine (**9**).[11] As illustrated in Scheme 3, the reaction of aldehyde **5** with **9** in boiling toluene gave the same regioselectivity that we observed with benzylhydroxylamine. The nitrone **10** was once again a transient intermediate and gave three cycloadducts, which were isolated in pure state by column chromatography. NMR data were consistent with two diastereoisomeric bridged-ring structures and one fused-ring structure, but did not allow the assignment of the configurations of the new stereocentres. The X-ray crystal structure analysis of the major product **11** (Fig. 1) revealed an absolute configuration α*R*,6*S*,9*R* and indirectly proved that of its diasteroisomer **12**. Unfortunately, compound **13** gave no crystals suitable for X-ray analysis and its absolute configuration remains undetermined.[10]



Scheme 3. Intramolecular cyloaddition of nitrone **10**.

using (*R*)-α-phenylethylhydroxylamine. Treatment of aldehyde **5** with benzylhydroxylamine in refluxing toluene formed the expected nitrone **6**, which directly underwent the intramolecular cycloaddition (Scheme 2). After 24 h, working and chromatography gave two regioisomeric cycloadducts in excellent overall yield. On the basis of the NMR data, the major product was assigned as the bridged-ring structure **7** and the minor one, the fused-ring structure **8**.[10] Both cycloadducts show a *cis* relationship of the two new stereocentres as a consequence of the intramolecular nature of the reaction, which suffers from a severe geometric restraint between dipole and dipolarophile.

Subsequently, with the aim of having in hand non-racemic

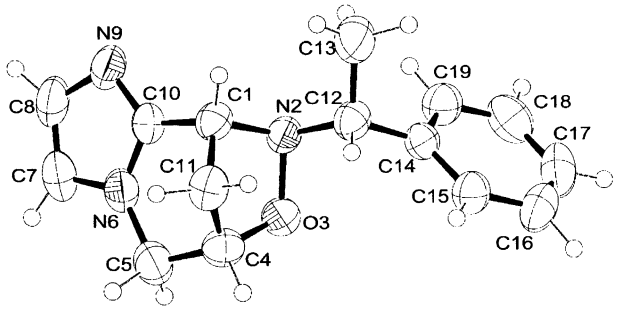


Figure 1. ORTEPIII plot of **11** determined by X-ray analysis. Thermal ellipsoids at 50% probability level, hydrogen atoms not to scale.

The regiochemical outcome of the above intramolecular cycloadditions is characterized by the large predominance of bridged-ring cycloadducts. This striking feature takes a determinant role in the light of our planned target. A possible explanation of the experimental finding relies upon the greater proximity of the reactant groups in the approach-type **A**, where the allyl pendant is bent towards the inside, with respect to **B** where the allyl pendant is disposed outside (Fig. 2). Consequently, the conformer **A**, although less thermodynamically favoured due to its crowding, could be more reactive than **B**.

To support this view, which engages mainly conformational factors and only marginally electronic effects, MM^+ calculations were done on the substrate **6** by taking into account different asyncronous pathways for each of the two possible orientations. Table 1 summarizes the energy data obtained on imposing various distances between the reaction centres.

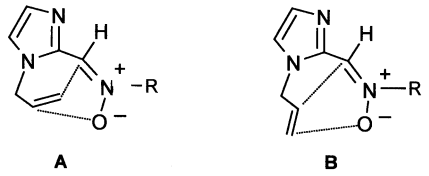


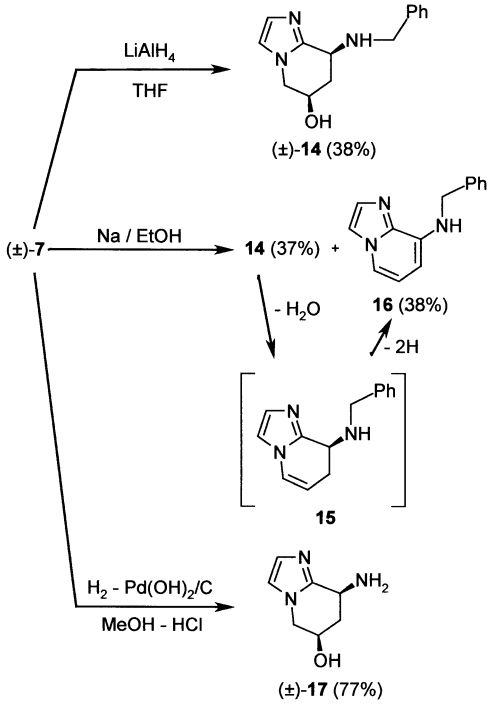
Figure 2. Regioisomeric approaches for the intramolecular cycloaddition of nitrones **6** and **10**.

Table 1. MM^+ calculations for approach-types **A** and **B**

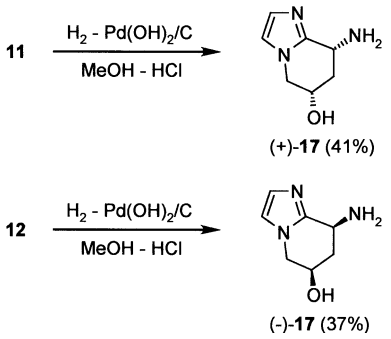
Distance between atoms (Å)	Energy (kcal/mol)	
	Approach-type **A**	Approach-type **B**
C–O=3.0; C–C=2.7	26.1	24.8
C–O=2.7; C–C=3.0	23.2	23.1
C–O=2.8; C–C=2.6	27.6	27.2
C–O=2.6; C–C=2.8	25.3	25.4
C–O=2.7; C–C=2.5	30.0	30.3
C–O=2.5; C–C=2.7	27.4	28.0

Two important deductions follow from such data: (i) a concerted mechanism, where the C–O bond formation is more advanced than the C–C one, is favoured for all orientations and distances; (ii) the competition between the two approach-types **A** and **B** is dependent on the distances considered, but the first approach becomes the more stable on shortening the distance between the reactant atoms, i.e. on setting out for the transition state. Based on these, the preferred formation of the bridged-ring cycloadduct may find rationalization.

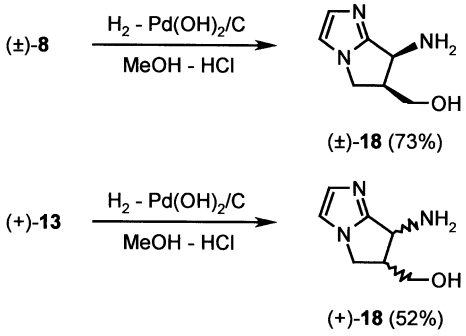
The second part of the present report is concerned with the manipulation of the cycloadducts aimed to achieve functionalised imidazo[1,2-*a*]pyridines. Among the plethora of reductive conditions used to open the isoxazolidine ring,[7] we tested those illustrated in Scheme 4. Lithium aluminium hydride treatment of **7** furnished the *N*-benzylated aminoalcohol **14** in moderate yield. When sodium in ethanol was used, we obtained the same product accompanied by a sizeable amount of the fully aromatic compound **16**, plausibly due to the dehydration of **14** followed by spontaneous oxidation of the dihydropyridine species **15**. The best result was accomplished by catalytic



Scheme 4. Reduction reactions of cycloadduct **7**.



Scheme 5. Hydrogenation reactions of cycloadducts **11** and **12**.



Scheme 6. Hydrogenation reactions of cycloadducts **8** and **13**.

hydrogenation with $Pd(OH)_2/C$ in the presence of protic catalysis. Under these conditions, the expected racemic aminoalcohol **17** was isolated in excellent yield. At this point, the catalytic hydrogenation of the diastereoisomeric cycloadducts **11** and **12** provided both enantiomers of **17** (Scheme 5). Their enantiomeric purity was proven to be total, within the experimental error limits, by means of the ^1H NMR spectra of (±)-**17**, (+)-**17** and (−)-**17** taken at 300 MHz in the presence of (*R*)-*O*-acetylmandelic acid.

It remains to be said that the minor fused-ring cycloadducts **8** and **13** underwent catalytic hydrogenation to give, respectively, the racemic pyrrolo[1,2-*a*]imidazole aminoalcohol **18** and one enantiomer of it with undetermined configuration (Scheme 6).

3. Conclusion

6,8-Bifunctionalised 5,6,7,8-tetrahydro-imidazo[1,2-*a*]-pyridines, both racemic and enantiopure, are accessible by a synthetic sequence which involves as the key step the intramolecular cycloaddition of nitrones derived from 1-allyl-2-imidazolecarbaldehyde. The regiochemical outcome of the cycloaddition, i.e. the largely predominant formation of bridged-ring cycloadducts, is the leading feature for the construction of the target system and therefore represents a stringent requisite for the general applicability of the synthetic approach described in this paper.

4. Experimental

4.1. General

Preparative column chromatography was carried out on silica gel 60 (Merck) (mesh size 63–200 μm). Melting points were measured on a Büchi B-540 heating unit and are not corrected. NMR spectra were recorded on an AVANCE 400 Bruker. Chemical shifts are reported in ppm relative to $CHCl_3$ (^1H=7.26) and $CDCl_3$ (^{13}C=77.0) as internal standard. Mass spectra were determined on a WG-70EQ instrument. IR spectra were taken on a FT-IR Perkin–Elmer 1725X spectrophotometer. Optical rotations were measured on a Perkin–Elmer 241 polarimeter.

4.1.1. 1-Allyl-2-hydroxymethylimidazole (4). A solution of 1-allylimidazole (5.0 mL, 46.3 mmol), trioxane (8.46 g, 94 mmol) and AcOH (0.5 mL) in DMSO (30 mL) was stirred at 130°C for 60 h. After cooling to room temperature and addition of water (70 mL), the mixture was adjusted to pH 9 with 32% aqueous ammonia and extracted with AcOEt. The organic layer was dried over Na_2SO_4, the solvent was evaporated under reduced pressure and the residue was chromatographed on a silica gel column with $CHCl_3$/MeOH 9:1 as eluent to give 2.55 g (40%) of **4**. Oil. ^1H NMR (300 MHz, $CDCl_3$): δ=2.20 (1H, br s, missing after deuteriation), 4.59 (2H, s), 4.61–4.65 (2H, m), 5.05 (1H, dd, J=1.1, 17.0 Hz), 5.20 (1H, dd, J=1.1, 10.3 Hz), 5.93 (1H, ddt, J=5.5, 10.3, 17.0 Hz), 6.81 (1H, d, J=1.1 Hz), 6.86 (1H, d, J=1.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=54.8 (t), 56.3 (t), 116.3 (t), 125.8 (d), 128.7 (d), 138.7 (d), 147.8 (s). MS: m/z 138 (M^+). IR: ν 3340 cm^{-1}. $C_7H_{10}N_2O$ (138.2): calcd C 60.85, H 7.30, N 20.27; found C 61.02, H 7.44, N 20.14.

4.1.2. 1-Allyl-2-imidazolecarbaldehyde (5). A suspension of **4** (2.50 g, 18.1 mmol) and MnO_2 (22.62 g, 260 mmol) in $CHCl_3$ (90 mL) was stirred at 60°C for 24 h. After filtration through celite, the solvent was removed under reduced pressure and the crude product was purified by chromatographic silica gel column with $CHCl_3$/MeOH 9:1 as eluent to give 670 mg (37%) of **5**. Oil. ^1H NMR (300 MHz, $CDCl_3$): δ=4.98–5.12 (2H, m), 5.11 (1H, dd, J=1.1, 16.2 Hz), 5.25 (1H, dd, J=1.1, 10.1 Hz), 5.77 (1H, ddt, J=5.7, 10.1, 16.2 Hz), 7.16 (1H, s), 7.30 (1H, s), 9.81 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ=50.1 (t), 119.1 (t), 126.4 (d), 132.1 (d), 132.8 (d), 143.6 (s), 182.4 (d). MS: m/z 136 (M^+). IR: ν 1690 cm^{-1}. $C_7H_8N_2O$ (136.2): calcd C 61.75, H 5.92, N 20.57; found C 61.72, H 6.09, N 20.38.

4.1.3. Reaction between 5 and *N*-benzylhydroxylamine. A suspension of *N*-benzylhydroxylamine hydrochloride (0.83 g, 5.2 mmol), $MgSO_4$ (9.00 g) and $NaHCO_3$ (1.00 g, 12 mmol) in toluene (120 mL) was stirred for 10 min, then a solution of **5** (0.60 g, 4.4 mmol) in toluene (10 mL) was added. The mixture was heated under stirring for 24 h. After cooling, filtration and evaporation under reduced pressure left a residue which was chromatographed on a silica gel column with AcOEt as eluent. The first fraction gave 256 mg (24%) of (3aR^*,8bR^*)-1-benzyl-1,3a,4,8b-tetrahydro-3*H*-imidazo[1′,2′:1,2]pyrrolo[3,4-*c*]isoxazole (**8**) as a white solid. Mp 129–130°C (from diisopropyl ether). ^1H NMR (300 MHz, $CDCl_3$): δ=3.87 (1H, dd, J=3.2, 8.9 Hz), 3.94–4.02 (2H, overlapping), 4.15–4.25 (4H, overlapping), 4.55 (1H, br s), 6.86 (1H, s), 7.17 (1H, s), 7.28–7.35 (3H, m), 7.44 (2H, d, J=7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=49.5 (t), 49.8 (d), 58.8 (t), 64.9 (d), 72.4 (t), 114.8 (d), 127.2 (d), 128.4 (d), 128.7 (d), 134.7 (d), 137.5 (s), 150.8 (s). MS: m/z 241 (M^+). IR (nujol): ν 1605, 1270, 750 cm^{-1}. $C_{14}H_{15}N_3O$ (241.3): calcd C 69.69, H 6.27, N 17.41; found C 69.57, H 6.46, N 17.46. The second fraction contained 650 mg (61%) of (6R^*,9S^*)-8-benzyl-5,6,8,9-tetrahydro-6,9-methanoimidazo[2,1-*d*][1,2,5]oxadiazepine (**7**) as colourless crystals. Mp 150–151°C (from diisopropyl ether). ^1H NMR (300 MHz, $CDCl_3$, 55°C): δ=2.21 (1H, d, J=11.5 Hz), 2.76 (1H, dt, J=5.6, 11.1 Hz), 3.49 (1H, br s), 3.86–3.91 (2H, overlapping), 4.02 (1H, dd, J=2.0, 12.5 Hz), 4.43 (1H, d, J=4.4 Hz), 4.79 (1H, d, J=6.2 Hz), 6.80 (1H, s), 6.99 (1H, s), 7.18–7.40 (5H, overlapping). ^{13}C NMR (100 MHz, $CDCl_3$, room temperature): *major conformer*: δ=36.4 (t), 52.8 (t), 57.7 (d), 59.7 (t), 72.7 (d), 118.7 (d), 119.2 (d), 127.8 (d), 128.7 (d), 128.8 (d), 129.0 (d), 129.4 (d), 137.8 (s), 144.9 (s); *minor conformer*: δ=32.1 (t), 52.1 (t), 58.1 (d), 63.5 (t), 73.8 (d), 115.2 (d), 119.1 (d), 127.8 (d), 128.7 (d), 128.8 (d), 129.0 (d), 129.4 (d), 137.8 (s), 144.9 (s). MS: m/z 241 (M^+). IR (nujol): ν 1605, 1300, 740 cm^{-1}. $C_{14}H_{15}N_3O$ (241.3): calcd C 69.69, H 6.27, N 17.41; found C 69.73, H 6.18, N 17.24.

4.1.4. Reaction between 5 and (*R*)-*N*-(α-phenylethyl)-hydroxylamine. A suspension of (*R*)-*N*-(α-phenylethyl)-hydroxylamine (1.19 g, 8.7 mmol), **5** (1.06 g, 7.8 mmol) and $MgSO_4$ (16.00 g) in toluene (120 mL) was heated under stirring for 24 h. After cooling, filtration and evaporation under reduced pressure left a residue which was chromatographed on a silica gel column with AcOEt/light petroleum/EtOH 7:2:1 as eluent. The first fraction gave 99 mg (5%) of (+)-1-(α-phenylethyl)-1,3a,4,8b-tetrahydro-3*H*-imidazo[1′,2′:1,2]pyrrolo[3,4-*c*]isoxazole (**13**) as a white solid. Mp 79–80°C (from diisopropyl ether). ^1H NMR (300 MHz, $CDCl_3$, 55°C): δ=1.61 (3H, d, J=6.4 Hz), 3.85–4.24 (6H, overlapping), 4.71 (1H, d, J=7.0 Hz), 6.83 (1H, s), 7.19 (1H, s), 7.27–7.48 (5H, overlapping). ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.4 (q), 49.4 (d), 50.4 (t), 62.8 (d), 63.4 (d), 72.9 (t), 115.0 (d), 127.9 (d), 129.1 (d), 135.4 (d), 143.1 (s), 151.2 (s). MS: m/z 255 (M^+). IR (nujol): ν 1605, 1285, 750 cm^{-1}. $[\alpha]_D^{22}$=+48.6 (c=0.091, $CHCl_3$). $C_{15}H_{17}N_3O$ (255.3): calcd C 70.56, H 6.71, N 16.46; found C 70.69, H 6.54, N 16.64. The second fraction furnished 676 mg (34%) of (α*R*,6*S*,9*R*)-8-(α-phenylethyl)-5,6,8,9-tetrahydro-6,9-methanoimidazo[2,1-*d*][1,2,5]oxadiazepine (**11**) as colourless crystals. Mp 125–126°C (from diisopropyl ether). ^1H NMR (300 MHz, $CDCl_3$): δ=1.45 (3H, d, J=5.4 Hz), 2.19 (1H, d, J=11.5 Hz), 2.84 (1H, br s), 3.23 (1H, br s), 3.92 (1H, br d, J=12.3 Hz), 4.07 (1H, br d, J=12.3 Hz), 4.44 (1H, br s), 4.84 (1H, d, J=6.3 Hz), 6.86 (1H, s), 7.05 (1H, s), 7.24–7.38 (5H, overlapping). ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.6 (q), 35.3 (t), 52.6 (t), 56.1 (d), 64.9 (d), 72.6 (d), 118.7 (d), 127.8 (d), 128.2 (d), 128.7 (d), 128.9 (d), 143.1 (s), 145.2 (s). MS: m/z 255 (M^+). IR (nujol): ν 1605, 1295, 740 cm^{-1}. $[\alpha]_D^{22}$=+68.3 (c=0.10, $CHCl_3$). $C_{15}H_{17}N_3O$ (255.3): calcd C 70.56, H 6.71, N 16.46; found C 70.55, H 6.58, N 16.60. The third fraction contained 258 mg (13%) of (α*R*,6*R*,9*S*)-8-(α-phenylethyl)-5,6,8,9-tetrahydro-6,9-methanoimidazo[2,1-*d*][1,2,5]oxadiazepine (**12**). Oil. ^1H NMR (300 MHz,

$CDCl_3$, 55°C): δ=1.48 (3H, d, J=6.5 Hz), 2.17 (1H, d, J=8.9 Hz), 2.73 (1H, br s), 3.28 (1H, br s), 3.85 (1H, dd, J=1.5, 12.5 Hz), 3.99 (1H, dd, J=2.0, 12.5 Hz), 4.54 (1H, br s), 4.78 (1H, d, J=6.2 Hz), 6.83 (1H, s), 7.01 (1H, s), 7.20–7.33 (5H, overlapping). ^{13}C NMR (100 MHz, $CDCl_3$, 55°C): δ=22.2 (q), 34.1 (t), 52.5 (t), 56.0 (d), 66.2 (d), 72.6 (d), 118.8 (d), 127.4 (d), 127.7 (d), 128.2 (d), 128.7 (d), 128.9 (d), 144.0 (s), 145.6 (s). MS: m/z 255 (M^+). IR (nujol): ν 1605, 1300, 740 cm^{-1}. $[\alpha]_D^{22}$=+44.9 (c=0.13, $CHCl_3$). $C_{15}H_{17}N_3O$ (255.3): calcd C 70.56, H 6.71, N 16.46; found C 70.73, H 6.58, N 16.29.

4.1.5. Reaction of 7 with $LiAlH_4$. A solution of $LiAlH_4$ (100 mg, 2.6 mmol) and **7** (100 mg, 0.41 mmol) in THF (5 mL) was stirred under nitrogen at 60°C for 24 h. The mixture was treated with MeOH (20 mL), aqueous AcONa 2.4 M (10 mL) and then extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel column with CH_2Cl_2/MeOH 9:1 as eluent to give 37 mg (38%) of (6R^*,8S^*)-8-benzylamino-6-hydroxy-5,6,7,8-tetrahydro-imidazo[1,2-a]pyridine (**14**) as a white solid. Mp 116–117°C (from diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.85 (1H, ddd, J=2.1, 4.0, 14.6 Hz), 2.54 (1H, ddd, J=2.0, 3.5, 14.6 Hz), 3.21 (2H, br s, missing after deuteriation), 3.86, 4.01 (2H, AB, J=12.7 Hz), 3.97 (1H, dd, J=3.2, 12.9 Hz), 4.18–4.27 (2H, overlapping), 4.41 (1H, br s), 6.82 (1H, s), 7.03 (1H, s), 7.18–7.30 (5H, overlapping). ^{13}C NMR (100 MHz, $CDCl_3$): δ=29.4 (t), 50.8 (d), 51.7 (t), 53.1 (t), 65.4 (d), 119.8 (d), 127.8 (d), 128.6 (d), 128.8 (d), 129.1 (d), 138.8 (s), 144.5 (s). MS: m/z 243 (M^+). IR (nujol): ν 3320, 2905 cm^{-1}. $C_{14}H_{17}N_3O$ (243.3): calcd C 69.11, H 7.04, N 17.27; found C 69.09, H 6.88, N 17.31.

4.1.6. Reaction of 7 with Na in EtOH. To a solution of **7** (100 mg, 0.41 mmol) in absolute EtOH (5 mL), sodium (150 mg, 6.5 mmol) was added portionwise under nitrogen. After stirring at room temperature for 5 h, EtOH (20 mL) was added and the mixture was evaporated under reduced pressure. The residue was taken with water (15 mL) and extracted with AcOEt. The organic layer was dried over Na_2SO_4, evaporated under reduced pressure and the residue was chromatographed on silica gel column with AcOEt/MeOH 1:1 as eluent. The first fraction gave 35 mg (38%) of 8-benzylamino-imidazo[1,2-a]pyridine (**16**) as a white solid. Mp 102–103°C (from diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.50 (2H, d, J=5.7 Hz), 5.80 (1H, br s, missing after deuteriation), 6.06 (1H, d, J=7.4 Hz), 6.61 (1H, t, J=7.1 Hz), 7.28–7.54 (7H, overlapping). ^{13}C NMR (100 MHz, $CDCl_3$): δ=47.8 (t), 97.9 (d), 113.9 (d), 114.1 (d), 114.9 (d), 127.7 (d), 129.0 (d), 131.5 (d), 137.5 (s), 138.8 (s). MS: m/z 223 (M^+). IR (nujol): ν 3425, 1565, 1265, 740 cm^{-1}. $C_{14}H_{13}N_3$ (223.3): calcd C 75.31, H 5.87, N 18.82; found C 75.23, H 6.05, N 18.81. The last fraction contained 39 mg (37%) of **14**.

4.2. General procedure for the hydrogenation reaction of cycloadducts

A mixture of 10% $Pd(OH)_2$/C (110 mg, 0.078 mmol) and isoxazolidinic compound (0.41 mmol) in a 0.06N solution of HCl in MeOH (15 mL) was stirred under H_2 for 24 h. After filtration through celite, the solvent was removed under reduced pressure. The residue was treated with 0.2 M aqueous KOH (5 mL) and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was chromatographed on silica gel column as indicated below.

4.2.1. Hydrogenation of 7. Elution with $CHCl_3$/MeOH 2:1 gave (6R^*,8S^*)-8-amino-6-hydroxy-5,6,7,8-tetrahydro-imidazo[1,2-a]pyridine (**17**) as a white solid. Yield: 77%. Mp 169–170°C (from diisopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.01 (1H, ddd, J=2.2, 3.3, 14.3 Hz), 2.27 (1H, ddd, J=2.2, 4.5, 14.3 Hz), 2.35 (3H, br s, missing after deuteriation), 3.98 (1H, dd, J=3.3, 12.9 Hz), 4.24 (1H, dd, J=3.8, 12.9 Hz), 4.43–4.48 (1H, m), 4.56 (1H, dd, J=3.3, 4.5 Hz), 6.87 (1H, d, J=1.1 Hz), 7.09 (1H, d, J=1.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=33.4 (t), 44.3 (d), 52.6 (t), 65.0 (d), 119.0 (d), 128.8 (d), 148.1 (s). MS: m/z 153 (M^+). IR (nujol): ν 3315, 2920, 2860, 1615, 1280, 730 cm^{-1}. $C_7H_{11}N_3O$ (153.2): calcd C 54.89, H 7.24, N 27.43; found C 55.03, H 7.18, N 27.51.

4.2.2. Hydrogenation of 11. Elution with $CHCl_3$/MeOH 2:1 gave (+)-(6S,7R)-**17**. Yield: 41%. $[\alpha]_D^{22}$=+8.3 (c=0.08, $CHCl_3$).

4.2.3. Hydrogenation of 12. Elution with $CHCl_3$/MeOH 2:1 gave (−)-(6R,7S)-**17**. Yield: 37%. $[\alpha]_D^{22}$=−11.4 (c=0.10, $CHCl_3$).

4.2.4. Hydrogenation of 8. Elution with $CHCl_3$/MeOH/NH_3 20:1:1 gave (6R^*,7S^*)-7-amino-6,7-dihydro-6-hydroxymethyl-5H-pyrrolo[1,2-a]imidazolo (**18**). Yield: 73%. Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.1–3.0 (3H, br s, missing after deuteriation), 3.07–3.19 (1H, m), 3.81 (1H, dd, J=6.6, 11.7 Hz), 3.89–4.02 (3H, overlapping), 4.52 (1H, d, J=7.7 Hz), 6.84 (1H, d, J=1.1 Hz), 7.06 (1H, d, J=1.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=45.9 (t), 46.5 (d), 49.4 (d), 61.7 (t), 115.2 (d), 133.7 (d), 156.2 (s). MS: m/z 153 (M^+). IR: ν 3365, 2960, 2920, 1600, 1260, 800 cm^{-1}. $C_7H_{11}N_3O$ (153.2): calcd C 54.89, H 7.24, N 27.43; found C 54.83, H 7.42, N 27.29.

4.2.5. Hydrogenation of 13. Elution with $CHCl_3$/MeOH/NH_3 20:1:1 gave (+)-**18**. Yield: 52%. $[\alpha]_D^{22}$=+2.76 (c=0.16, $CHCl_3$).

4.3. X-Ray crystallographic analysis of 11

Single-crystal X-ray diffraction measurements were performed on a Bruker APEX CCD diffractometer, graphite monochromator, Mo Kα radiation (λ=0.71073 Å). The crystal data are as follows: $C_{15}H_{17}N_3O$, M_r=255.32, orthorhombic, space group $P2_12_12_1$, a=9.4024 (9), b=11.0636 (10), c=12.5419 (12) Å, V=1304.7 (2) Å^3, Z=4, D_c= 1.300 g cm^{-3}, μ (Mo Kα)=0.084 mm^{-1}; 13,728 collected data (2θ<56°), 1815 unique [982 with $I_o>2\sigma(I_o)$], R_{ave}=0.0479. Structure was solved by direct methods (SIR-92)[12] and refined by full-matrix least-squares (SHELX-97).[13] The absolute configuration at C1 and C4 was assigned upon the known stereochemistry at C12 (Fig. 1); geometrical parameters of the molecule are in the

expected range; final disagreement factors for all (observed) reflections: $R_w(F^2)=0.0496(0.0466)$ and $R=0.0540(0.0287)$. All crystallographic data (excluding structure factors) were deposited to the Cambridge Crystallographic Data Center as supplementary publication No. CCDC 177068. Copies of the data can be obtained free of charge on application to CCDC, 2 Union Road, Cambridge CB2 1EZ, UK, e-mail deposit@ccdc.cam.ac.uk.

Acknowledgements

We are grateful to MURST and CNR for financial support.

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10. ^{1}H NMR spectra of **7** and **12**, as well as ^{13}C NMR spectrum of **12**, were little diagnostic at room temperature because of their broad and overlapping signals, while a better resolution was observed at 55°C. This may be due to the existence of two invertomers at the pyramidal nitrogen of the isoxazolidinic ring. Such conformers were really differentiated in the ^{13}C NMR spectrum of **7** where two sets of clear signals were evident.
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