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Synthesis and α4β2 nicotinic affinity of unichiral 5-(2-pyrrolidinyl)oxazolidinones and 2-(2-pyrrolidinyl)benzodioxanes

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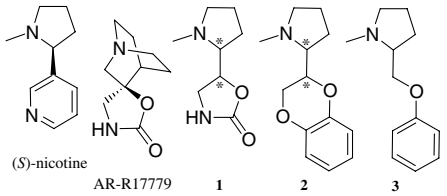
Abstract—The *RS* and *SR* enantiomers of 2-oxazolidinone and 1,4-benzodioxane bearing a 2-pyrrolidinyl substituent at the 5- and 2-position, respectively, were synthesized as candidate nicotinoids. One of the two benzodioxane stereoisomers reasonably fits the pharmacophore elements of (*S*)-nicotine and binds at α4β2 nicotinic acetylcholine receptor with submicromolar affinity. Interestingly, both the synthesized pyrrolidinylbenzodioxanes exhibit analogous affinity at α_2 adrenergic receptor resembling the behaviour of some known α_2-AR ligands recently proved to possess neuronal nicotinic affinity.

Neuronal nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels playing an important role in the regulation of neurotransmission in the CNS. Their dysfunction has been related to a number of severe brain pathologies, including Parkinson's and Alzheimer's diseases, schizophrenia, anxiety, and some forms of epilepsy. As a result, novel ligands for neuronal nAChRs, in particular for the two major α4β2 and α7 brain subtypes, may have a great potential as pharmaceuticals aiming at several neurological disorders.[1] Indeed, subtype selective nAChR ligands have been developed over the last decade leading to the formulation of reliable α4β2 and, more recently, α7 pharmacophores, where common elements are a cationic centre (N^+) and a suitably distanced hydrogen bond acceptor and/or π-electron-rich group (HBA/π), while a distinctive element enhancing α7 binding properties seems to be a bulky hydrophobic moiety directly attached to the cationic nitrogen containing portion or to HBA/π.[2–4] The directionality of the HBA/π group relative to the $N^+ \rightarrow$ HBA/π vector emerges as a critical feature and there is a continuing interest concerning nicotine and novel nicotinoids with only one or no rotatable bond between the cationic centre and HBA/π as useful ligand templates. Recently, we have reported unichiral *E* and *Z* isomers of pyrrolidinylmethoxyimines and prolinal oxime ethers as candidate bioisosteres of nicotine and its isoxazolic analogue ABT 418, demonstrating that some of them display a submicromolar α4β2 affinity and a remarkable selectivity over α7 and muscarinic receptors.[5] In a continuation of this investigation, we present here the synthesis and the nicotinic binding affinity of **1** and **2**, where the typical nicotinoid 2-pyrrolidinyl residue is linked to a HBA/π cyclic moiety, represented by oxazolidin-2-one and 1,4-benzodioxane, respectively.



Both the designed structures are characterized by the presence of two vicinal stereocentres connected by the only bond, whose rotation is relevant to molecule

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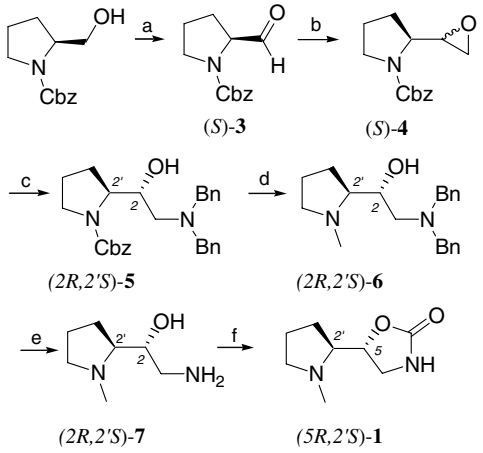
conformation. In view of finding ligands with diversified affinity profiles, this was judged an intriguing feature in addition to the existence of four different isomers and to the fact that such a stereochemical complication takes place in proximity of the critical cationic head with predictably important consequences on the mutual disposition of N^+ and HBA/π. The replacement of the HBA/π moiety of nicotine, namely the pyridine ring, by oxazolidin-2-one and 1,4-benzodioxane was undertaken considering the HBA/π properties of both these systems. Furthermore, in the case of oxazolidinone, we considered the reported successful combination of the cyclic carbamate with quinuclidine to give a conformationally restricted spiranic analogue of acetylcholine (AR-R17779) with high and specific α7 nicotinic affinity[6,7] and, in the case of benzodioxane, the chance of creating a partially rigidified analogue of prolinol phenyl ethers (**3**), whose nicotinic affinity is well known.[8] To our knowledge, the use of benzodioxane system in nicotinic ligands was limited to 6-(2-pyrrolidinyl)-1,4-benzodioxane[9] and 3-quinuclidinyl 1,4-benzodioxan-5-carboxyamide,[10] where benzodioxane is linked to the rest of the molecule through the benzene ring and represents, in the case of quinuclidine derivative, the additional bulky hydrophobic moiety typical of many candidate α7 ligands.

The synthesis of (5*R*,2′*S*)-5[1′-methylpyrrolidin-2′-yl]-1,3-oxazolidin-2-one [(5*R*,2′*S*)-**1**] was accomplished as outlined in Scheme 1. (*S*)-*N*-Carbobenzyloxyprolinol was oxidized to the corresponding aldehyde (*S*)-**3** with sulfur trioxide pyridine complex as previously reported in the literature.[11] The aldehyde was then converted into a nearly equimolar diastereomeric mixture of *R*,*S* and *SS* (1-carbobenzyloxy-2-pyrrolidinyl)oxirane, epimers at the newly formed chiral centre, by treatment with dimethylsulfoxonium methylide.[12] As proved by ^{1}H NMR and HPLC analyses,[13] subsequent oxirane ring opening by dibenzylamine allowed only one diastereoisomer of secondary dibenzylaminoalcohol **5** to be isolated, namely that deriving from the *SS* pyrrolidinyloxirane and having *R* configuration at the exocyclic alcoholic carbon. The Cbz group of this novel synthetic intermediate was reduced to methyl with $LiAlH_4$ and the resulting diamine (2*R*,2′*S*)-**6**[14] debenzylated by hydrogenolysis to give (2*R*,2′*S*)-**7**,[15] which was finally cyclised to (5*R*,2′*S*)-**1** by reaction with 1,1′-carbonyldiimidazole. Three hundred mega hertz ^{1}H NMR spectra confirmed the unitary diastereoisomeric composition of the two last intermediates **6** and **7** and of the final pyrrolydinyloxazolidinone (5*R*,2′*S*)-**1**.[16] On the basis of the X-ray crystallographic analysis,[17] *R* configuration was assigned to the oxygen-bound asymmetric carbon of this latter and, retrospectively, of the three preceding aminoalcohols **5**–**7** (Fig. 1).

Starting from (*R*)-*N*-carbobenzyloxyprolinol, the same synthetic route illustrated in Scheme 1 led to (5*S*,2′*R*)-**1**.[19]

In order to obtain the pyrrolidinylbenzodioxane **2** with *S* configuration at the nitrogen-bound asymmetric carbon, the diastereomeric mixture of *R*,*S*, and *SS* (1-carbobenzyloxy-2-pyrrolidinyl)oxirane, epimers at the epoxide chiral centre, was reacted with 2-benzyloxyphenol and potassium carbonate in 2-propanol (Scheme 2). As in the previous oxirane opening with dibenzylamine, only one diastereomeric secondary alcohol resulted from the nucleophilic attack by phenoxyphenate, namely the *SS* phenoxyalcohol **8**,[20] where the four substituents at the oxygen-bound asymmetric carbon have the same reciprocal disposition as in (2*R*,2′*S*)-**5** with phenoxymethyl replacing dibenzylaminomethyl group. Upon this reaction, the N-protecting group was almost quantitatively transformed into isopropoxycarbonyl. From the above reaction, another main product was isolated and identified, on the basis of ^{1}H NMR and mass spectra, as the tetrahydropyrroloxazolone derivative **9**.[21] This latter product, which was not submitted to further synthetic transformations, also showed unitary diastereomeric composition and its configuration was tentatively established to be *R* and *S* at the oxygen- and nitrogen-bound stereogenic carbons, respectively, presuming that the bicyclic system was originated by



Scheme 1. Synthesis of pyrrolidinyloxazolidinone. Reagents and conditions: (a) pyridine–SO_3 complex, TEA, DMSO 25 °C, 2 h, 89%; (b) NaH, trimethylsulfoxonium iodide, DMSO, THF, 25 °C, 2 h, 40%; (c) dibenzylamine, 2-propanol, MW irradiation (150 °C, 100 W), 15 min, 48%; (d) $LiAlH_4$, THF, reflux, 2 h, 54%; (e) H_2–Pd/C, MeOH, 96 h, 100%; (f) 1,1′-carbonyldiimidazole, THF, reflux, 2 h, 58%.

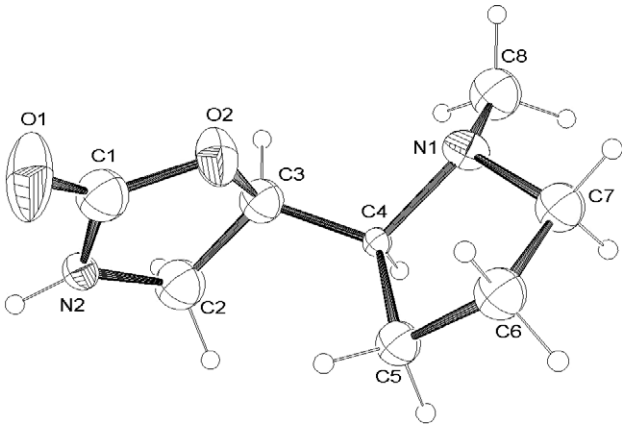
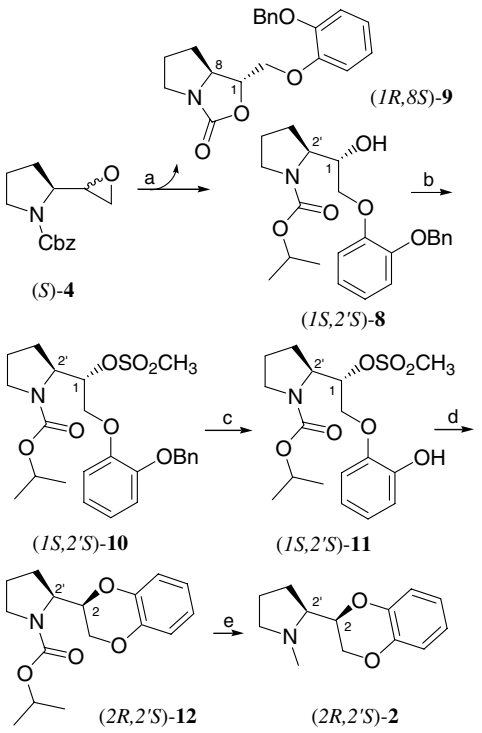


Figure 1. ORTEP[18] of (5*R*,2′*S*)-**1**, showing the atom-numbering scheme (ellipsoids are at the 40% probability).



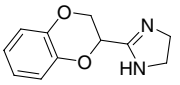
Scheme 2. Synthesis of pyrrolidinylbenzodioxane. Reagents and conditions: (a) 2-benzyloxyphenol, potassium carbonate, 2-propanol, reflux, 24 h, 42% for **8** and 30% for **9**; (b) Mesyl chloride, triethylamine, dichloromethane, 25 °C, 1 h, 95%; (c) H_2–Pd/C, EtOH, 24 h, 79%; (d) potassium carbonate, acetone, reflux, 24 h, 88%; (e) $LiAlH_4$, THF, reflux, 2 h, 82%.

the *RS* diastereomer of **4** through oxirane ring opening and subsequent intramolecular displacement of Cbz phenoxy group by oxirane oxygen. The benzyloxyphenoxyalcohol (1*S*,2′*S*)-**8** was mesylated and debenzylated. Successive intramolecular nucleophilic substitution of mesylate by the *ortho*-phenoxy moiety gave 1,4-dioxane ring closure [(2*R*,2′*S*)-**12**].[22] The isopropoxycarbonyl group was finally reduced to methyl obtaining (2*R*,2′*S*)-2[1′-methylpyrrolidin-2′-yl]-1,4-benzodioxane [(2*R*,2′*S*)-**2**] as an oily product, which was easily converted into its hydrochloride.[23] ^{1}H NMR analysis of vicinal coupling constants for (2*R*,2′*S*)-**2** showed the relative *anti* disposition of the benzodioxane methine proton not only to one of the two benzodioxane methylene protons, as imposed by chair conformation of dioxane ring and by equatorial position of 2-pyrrolidinyl substituent, but also to pyrrolidine methine proton. As proved by conformational analysis, such a double *anti* disposition of the three vicinal protons is favoured in the diastereomer with opposite configurations at the two asymmetric carbons, while the same arrangement is virtually forbidden, due to the steric hindrance between *N*-methyl and benzodioxane methylene, in the diastereomer with identical configurations at the two stereocentres. Therefore, *R* configuration was assigned to the benzodioxane C_2 of the diastereomer of **2** prepared from (*S*)-*N*-carbobenzyloxyprolinol. The absolute configuration of the same stereogenic carbon in the synthetic intermediates **8**–**12**, which are all novel synthetic intermediates, was consequently established by correlation to (2*R*,2′*S*)-**2** as reported in Scheme 2.

(2*S*,2′*R*)-**2** was prepared by the same synthesis as its enantiomer but starting from (*R*)-**4**, in turn obtained from (*R*)-*N*-carbobenzyloxyprolinol as a mixture of epimers at the epoxide chiral centre.[24]

For the reasons explained above, though the common intermediate **4** was a mixture of two diastereomers, the syntheses provided only the *u* stereoisomers of **1** and **2**. The *l* stereoisomers, that is, the *SS* and *RR* forms, were not obtained and the foreseen availability of all the four stereoisomers of both **1** and **2** was not realized. This notwithstanding, the biological evaluation was not deferred considering that the study of the two synthesized enantiomeric pairs could be already highly informative. In particular, we evaluated the affinity towards the α4β2 and the α7 subtypes present in rat cortex membranes by binding studies using, as ligands, [^{3}H]-epibatidine and [^{125}I]-αBungarotoxin, respectively.[25] Nicotine was included in the series for comparison. As shown in Table 1, we found that the two pyrrolidinyloxazolidinones are virtually devoid of nicotinic affinity, whereas the two pyrrolidinylbenzodioxanes exhibit α4β2 affinity. In particular, (2*R*,2′*S*)-**2**, which has the same *S* configuration at the pyrrolidine stereocentre as (−)-nicotine, shows a moderate submicromolar affinity for α4β2 nAChR and is fourfold more potent than its enantiomer. Both the isomers of **2** display a remarkable similar selectivity over the α7 nAChR.

Furthermore, the structural analogy between **2** and α_2-adrenergic receptor (α_2-AR) ligands such as efaroxan, imiloxan, and, especially, idazoxan induced to evaluate the binding of **2** also to α_2-ARs. Interestingly, we found that both (2*R*,2′*S*)-**2** and (2*S*,2′*R*)-**2** possess the ability to compete with [^{3}H]RS 79948-197 for rat cortex α_2-ARs displaying submicromolar affinities (0.77 and 0.47 μM K_i, respectively; K_d 1.01 nM).[26,27]



The lack of affinity of (5*R*,2′*S*)-**1** and (5*S*,2′*R*)-**1** for both α4β2 and α7 nAChRs is likely to be explained considering the different positions of the pharmacophore elements in pyrrolidinyloxazolidinone than in nicotine

Table 1. Affinity of nicotine and compounds **1**–**2** for native receptor subtypes, present in rat brain membranes, labelled by [^{3}H]-epibatidine and [^{125}I]-αBungarotoxin

Compound	[^{3}H]-Epi K_i (μM)	[^{125}I]-αBgtx K_i (μM)
(−)-Nicotine	0.004 (18)	0.234 (29)
(5*R*,2′*S*)-**1**	62 (17)	117 (34)
(5*S*,2′*R*)-**1**	80 (18)	338 (31)
(2*R*,2′*S*)-**2**·HCl	0.62 (18)	12 (33)
(2*S*,2′*R*)-**2**·HCl	2.57 (16)	45 (27)
K_d (nM)	0.020 (23)	1.06 (32)

The K_d and K_i values were derived from [^{3}H]-epibatidine and [^{125}I]-αBungarotoxin saturation and two competition binding experiments on rat brain membranes as described in Ref. 25. The curves were fitted using a nonlinear least squares analysis program and the *F* test. The numbers in brackets represent the %CV.

Table 2. Interatomic distances (Å) for **1** stereoisomers, root mean square (rms) deviations (Å) of the coordinates of the four selected matching atoms of **1** from those of the corresponding atoms of reference compounds ((*S*)-nicotine and AR-R17779) and distances (Å) between N^+ of **1** and N^+ of reference compounds

Compound[a]	N^+–N distance in **1**	N^+–CO distance in **1**	rms		N^+–N^+ distance **1**-nic.	N^+–N^+distance[b] **1**-AR-R17779
			nicotine	AR-R17779		
(5*R*,2′*R*)-**1**	4.76	5.21	0.45	0.35	0.21	0.30 (1.89)
(5*S*,2′*R*)-**1**	4.59	4.89	0.80	0.47	0.29	0.78 (2.50)
(5*R*,2′*S*)-**1**	4.68	5.04	0.90	0.33	0.31	0.72 (1.25)
(5*S*,2′*S*)-**1**	4.50	5.81	0.99	0.35	0.28	0.57 (1.32)

[a] *S* configuration was invariably given to the protonated nitrogen.
[b] In brackets, the distance between the two N^+ when the two oxazolidinone rings are allowed to exactly coincide.

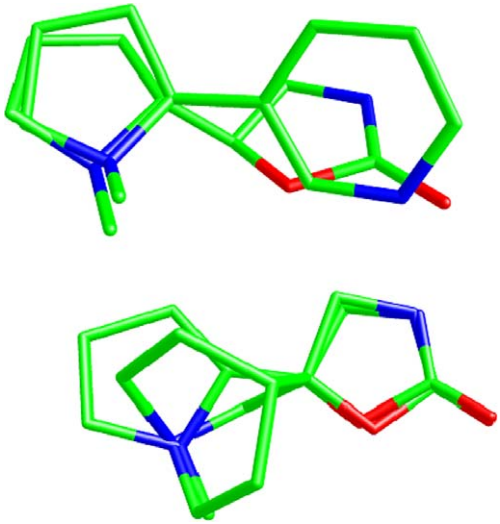


Figure 2. Superposition of (5*R*,2′*R*)-**1** onto (*S*)-nicotine and AR-R17779.

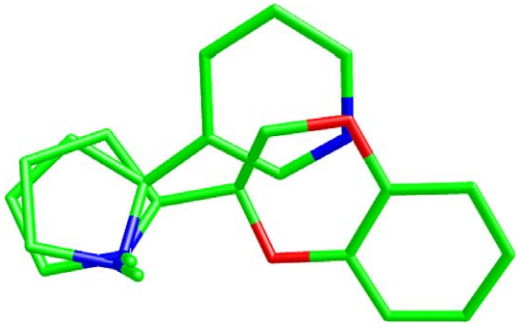


Figure 3. Superposition of (2*R*,2′*S*)-**2** onto (*S*)-nicotine.

and in AR-R17779. All the lowest energy conformers of the stereoisomers of **1**, which have in common a ≅60° angle between the two ring planes, as indicated by conformational analysis[28] and by X-ray analysis of (5*R*,2′*S*)-**1**, and N^+–HBA (N^+–N or N^+–CO) distances compatible with nicotinic pharmacophore models, are superimposed on nicotine with unfavourably high rms distance between the four selected matching atoms (methyl carbon, cationic nitrogen, pyrrolidine stereocentre, and carbonylic oxygen/pyridine nitrogen), with the only exception of the unfortunately unavailable *RR* isomer (0.45 Å rms distance and 0.21 Å N^+–N^+ distance) (Table 2 and Fig. 2). The superposition onto AR-R17779 (fitting of the four heteroatoms) is better, as shown by the generally lower rms values, but the N^+–N^+ distances are sensibly higher (Table 2). Also accounting that superposition through three atoms of oxazolidinone and the only cationic nitrogen helps in raising the distance between the N^+ atoms, nevertheless the positions of these latter are to be considered significantly different and become quite divergent when the oxazolidinone rings of **1** and AR-R17779 are allowed to exactly coincide. Again, it is the *RR* isomer that gives the best superposition of ammonium nitrogen atoms (Fig. 2).

In the case of pyrrolidinylbenzodioxanes **2**, contrary to pyrrolidinyloxazolidinones **1**, the lowest energy conformers[28] of the two synthesized enantiomers, *SR* and *RS*, are those showing the best superposition with nicotine with low rms distances (0.36 and 0.39, for (2*R*,2′*S*)-**2** and (2*S*,2′*R*)-**2**, respectively, versus 0.60 and 0.91 for the other two streoisomers; matching atoms: methyl carbon, cationic nitrogen, pyrrolidine stereocentre, and benzodioxane O(4)/pyridine nitrogen) (Table 3). This is consistent with the finding of nicotinic affinity. In particular, (2*R*,2′*S*)-**2**, which displays a submicromolar α4β2 affinity, shows, in addition to the minimum value of rms distance, the maximum closeness of O(4) to pyridine nitrogen of nicotine and a 4.68 Å N^+–O(4) distance. Both these features candidate O(4) of (2*R*,2′*S*)-**2** to

Table 3. Interatomic distances (Å) for **2** stereoisomers, root mean square (rms) deviations (Å) of the coordinates of the four selected matching atoms of **2** from those of the corresponding atoms of the reference compound (*S*)-nicotine and distances (Å) between O(4) of **2** and pyridine N of nicotine

Compound[a]	N^+–O(4) distance in **2**	rms	N(pyridine)–O(4) distance
(2*R*,2′*R*)-**2**	4.95	0.60	0.71
(2*S*,2′*R*)-**2**	3.42	0.39	0.76
(2*R*,2′*S*)-**2**	4.68	0.36	0.30
(2*S*,2′*S*)-**2**	4.34	0.91	0.78

[a] *S* configuration was invariably given to the protonated nitrogen.

replace pyridine nitrogen as HBA in the interaction with the binding site. As shown in Figure 3 for (2*R*,2′*S*)-**2**, the benzene ring, whose plane makes a ≅55° angle with the pyrrolidine plane, cannot overlay the pyridine ring of nicotine because condensed with dioxane; however, though entirely exceeding the overlap volume, it does not preclude the interaction.

Finally, we would like to draw attention to the α_2-AR affinity of pyrrolidinylbenzodioxanes. Recently, Abelson and Höglund[29] have demonstrated that α_2-AR ligands, such as clonidine, rilmenidine, and efaroxan, possess micromolar or submicromolar affinity for rat spinal cord receptors labelled by [^{3}H]epibatidine and affect spinal ACh release. Their observation would provide strong evidence to that nicotinic receptors are involved in the increase or decrease of intraspinal ACh produced by the α_2-AR ligands and in the antinociception mediated by these later. Proceeding in the opposite direction, we evidenced an analogous double-faced profile of binding affinity for a novel compound, namely (2*R*,2′*S*)-**2**, whose structure resembles that of α_2-AR ligand idazoxan. Our findings are consistent with Abelson's results, indicating the same interesting coexistence of affinities for two quite different receptor systems, an unexpected feature, which could be not undesirable.

Acknowledgments

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13. Compound (2*R*,2′*S*)-**5**: isolated as an oil after repeated chromatographic separations on silica gel (eluent 99:1 dichloromethane/methanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.50–1.90 (m, 4H), 2.35–2.60 (m, 2H), 3.20–4.20 (m, 8H), 5.00–5.20 (m, 2H), 7.15–7.45 (m, 15H). Analytical HPLC: LiChrospher 5 μm or μPorasil 10 μm column, 98:2 dichloromethane/methanol, 2 ml/min.
14. Compound (2*R*,2′*S*)-**6**: isolated as an oil by chromatography on silica gel (eluent: from 95:5 to 92:8 dichloromethane/methanol); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15–1.30 (m, 1H), 1.55–1.75 (m, 3H), 2.38 (s, 3H), 2.25–2.41 (m, 1H), 2.46–2.61 (m, 3H), 3.17–3.23 (m, 1H), 3.51 (d, J = 13.4 Hz, 2H), 3.72 (d, J = 13.4 Hz, 2H), 3.98 (t, 1H), 7.18–7.39 (m, 10H).
15. Compound (2*R*,2′*S*)-**7**: isolated as an oil by concentration of the reaction solution in methanol after removal of the catalyst; ^{1}H NMR ($CDCl_3$) δ 1.67–1.86 (m, 4H), 2.30–2.51 (m, 2H), 2.44 (s, 3H), 2.79 (d, J = 5.9 Hz, 2H), 3.15–3.18 (m, 1H), 3.62 (br s, 3H, disappears on exchange with D_2O), 3.82–3.91 (m, 1H).
16. Compound (5*R*,2′*S*)-**1**: mp 143–144 °C (isolated by chromatography on silica gel; eluent 80:20 toluene/methanol); $[\alpha]_D^{20}$ −66.5 (*c* 0.4, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.56–1.67 (m, 1H), 1.69–1.80 (m, 2H), 1.87–2.00 (m, 1H), 2.33 (pseudo q, J = 8.4 Hz, 1H), 2.42 (s, 3H), 2.62–2.68 (m, 1H), 3.05–3.11 (m, 1H), 3.51 (pseudo t, J = 8.4 Hz, 1H), 3.64 (pseudo t, J = 8.4 Hz, 1H), 4.66–4.73 (m, 1H), 5.80 (br s, 1H). Anal. Calcd for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.22; H, 8.36; N, 16.35.
17. Crystallographic data of **1** were obtained using an Enraf Nonius CAD-4 diffractometer (MoKα radiation) at room temperature. The structures were solved by direct methods [Altomare, A.; C. Burla, M.; Camalli, M.; Cascarano, G.; Giacovazzo, C.; Gagliardi, A.; Polidori, G. *J. Appl. Crystallogr.* **1994**, *27*, 435.] and the refinements were carried out by full-matrix least-squares using SHELX-97 [Sheldrick, G. M.; SHELX-97, University of Göttingen, Germany]. The absolute configuration of oxazolidinone asymmetric carbon was assigned on the basis of the known chirality of the pyrrolidine asymmetric centre. CCDC-616375 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk).
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19. Compound (5*S*,2′*R*)-**1**: $[\alpha]_D^{20}$ +56.5 (*c* 0.4, MeOH); mp and ^{1}H NMR identical to the enantiomer.
20. Compound (1*S*,2′*S*)-**8**: isolated as an oil by chromatography on silica gel (eluent: from 80:20 to 50:50 cyclohexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (d, J = 6.2 Hz, 6H), 1.68–2.04 (m, 3H), 2.12–2.22 (m, 1H), 3.20–3.30 (m, 1H), 3.40–3.55 (m, 2H), 3.98–4.03 (m, 2H), 4.07–4.15 (m, 1H), 4.90 (sp, J = 6.2 Hz, 1H), 5.08 (s, 2H),

6.88–6.97 (m, 4H), 7.29–7.43 (m, 5H). MS *m/z* 422.3 ($M+Na^+$); Analytical HPLC: μPorasil 10 μm column, 70:30 *n*-hexane/ethyl acetate, 1 ml/min.

21. Compound (1*R*,8*S*)-**9**: isolated as a white solid by chromatography on silica gel (eluent: from 80:20 to 50:50 cyclohexane/ethyl acetate); mp 117–119 °C;^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.49–1.65 (m, 1H), 1.70–1.90 (m, 2H), 1.95–2.10 (m, 1H), 3.11–3.19 (m, 1H), 3.52–3.61 (m, 1H), 3.91–3.99 (m, 1H), 4.15 (dd, 1H), 4.31 (dd, 1H), 5.00 (q, 1H), 5.08 (s, 2H), 6.87–6.96 (m, 4H), 7.27–7.45 (m, 5H). MS *m/z* 362.3 ($M+Na^+$). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.61; H, 6.31; N, 4.06.
22. Compound (2*R*,2′*S*)-**12**: obtained as an oil after removal of acetone, treatment of the resultant residue with water and ethyl acetate and concentration of the dried organic phase; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.24 (d, J = 6.2 Hz, 6H), 1.83–1.96 (m, 1H), 2.02–2.20 (m, 3H), 3.33–3.65 (m, 2H), 3.92 (dd, J = 9.2, 12.2 Hz, 1H), 4.20–4.44 (m, 3H), 4.90 (br s, 1H), 6.76–6.90 (m, 4H). Analytical HPLC: μPorasil 10 μm column, 70:30 *n*-hexane/ethyl acetate, 1 ml/min.
23. Compound (2*R*,2′*S*)-**2**: isolated as an oil by chromatography on silica gel (eluent: 92:8 dichloromethane/methanol); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.66–1.86 (m, 3H), 1.87–2.03 (m, 1H), 2.28–2.49 (m, 1H), 2.52 (s, 3H), 2.65–2.72 (m, 1H), 3.13–3.19 (m, 1H), 4.00 (dd, J= 11.0, 7.0 Hz, 1H), 4.22 (dt, J = 7.0, 2.2 Hz, 1H), 4.29 (dd, J = 11.0, 2.2 Hz, 1H), 6.78–6.91 (m, 4H). Analytical HPLC: μPorasil 10 μm column, 95:5:0.6 dichloromethane/methanol/NH_3, 1 ml/min. (2*R*,2′*S*)-**2** Hydrochloride: mp 190–193 °C (ethanol); $[\alpha]_D^{20}$ +20.3 (*c* 2.0, EtOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.82–2.19 (m, 4H), 2.88 (s, 3H), 3.05–3.16 (m, 1H), 3.50–3.65 (m, 2H), 4.11 (dd, J = 12.1, 5.5 Hz, 1H), 4.31 (d, J = 12.1 Hz, 1H), 4.70–4.79 (m, 1H), 6.85–6.96 (m, 4H), 11.12 (br s, 1H). Anal. Calcd for $C_{13}H_{18}ClNO_2$: C, 61.06; H, 7.09; Cl, 13.86; N, 5.48. Found: C, 60.84; H, 7.01; Cl, 13.69; N, 5.43.
24. Compound (2*S*,2′*R*)-**2**: ^{1}H NMR spectrum identical to (2*R*,2′*S*)-**2**. (2*S*,2′*R*)-**2** Hydrochloride: $[\alpha]_D^{20}$ −17.8 (*c* 2.0, EtOH); mp and ^{1}H NMR identical to the enantiomer.
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28. The stereoisomers of **1** and **2** were built in their protonated form using the VEGA program (freely downloadable at www.ddl.unimi.it). Their conformational analyses were performed systematically rotating the interannular rotatable bond (yielding 360 conformers) and minimizing the obtained conformers to avoid high-energy geometries (conjugate gradients until rms = 0.01). The calculations were carried out using Quanta/CHARMm package (MSI, Burlington, MA) with the force-field CHARMm v22 and the atomic charges calculated by Gasteiger's method.
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