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Analogs of the dopamine D4 receptor ligand FAUC 113 with planar- and central-chirality

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Abstract—By employing yeast enzymes, natural amino acids and the Jacobsen's catalyst as sources of chirality, we have synthesized pyrazolo[1,5-*a*]pyridine derivatives with central- and planar-chirality as analogs of the dopamine D4 receptor ligand FAUC 113. In vitro binding experiments displayed enhanced D2 and D3 affinity for both enantiomers of the [2.2]paracyclophane **3**. The *C*-methylpiperazine (*R*)-**4a** revealed excellent D4 selectivity.

1. Introduction

The successful cloning of the dopamine D4 receptor subtype in the early 1990s[1] marked the beginning of an extensive search for subtype selective ligands. These investigations were inspired by the assumption that neurotransmission at the D4 receptor is associated with the neuropathology of schizophrenia, attention-deficit hyperactivity (ADHD), mood disorders and Parkinson's disease.[2] It is interesting to note that compounds fulfilling the structural specifications of type A in particular (see Fig. 1) proved to be extremely potent D4 receptor ligands.[3] Following these requirements, we recently reported on the highly selective D4 receptor partial agonist FAUC 113 revealing D4 affinity in the low nanomolar range.[4] Structural modification led to the regioisomer FAUC 213 showing a full antagonist profile.[5] In contrast, introduction of a cyano substituent into position 7 of the pyrazolo[1,5-*a*]pyridine moiety (FAUC 327) significantly increased the intrinsic activity.[6] As we are planning non-invasive investigations of D4-neurotransmission by SPECT, we synthesized and evaluated the radiolabelled 7-iodo analog **1**.[7] Although stereocontrolled recognition processes have received much attention in modern drug discovery, none of the D4 receptor ligands of type A that were previously described feature chiral information. Very recently, we reported on the asymmetric synthesis and biological effects of the first planar-chiral neuroreceptor ligands (*R*)-**2** and (*S*)-**2** incorporating a hitherto unknown indolocyclophane as a structural feature,[8] when significant dopamine receptor subtype specific stereodifferentiation was observed.[9]

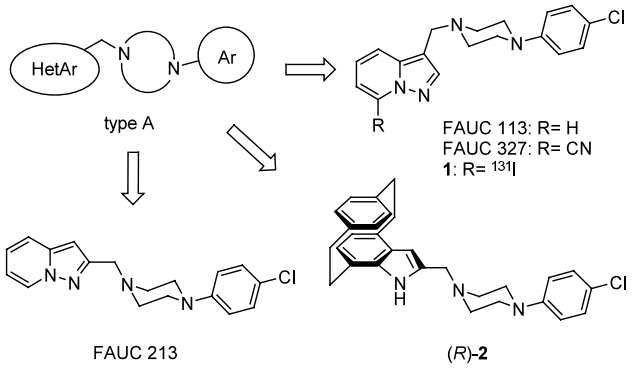

Figure 1. Arylpiperazinyl substituted heteroarenes as potent dopamine D4 receptor ligands.

As an extension of these studies investigating the influence of the absolute configuration on the ligand recognition at the dopamine receptors we designed a number of central- and planar-chiral FAUC 113 analogs. Variations of the structural moieties of type A should be performed by replacement of the chlorophenyl group with the [2.2]paracyclophane system resulting in the target compound **3** (Fig. 2). Introduction of a methyl group into the piperazine moiety and its complete exchange for alternative asymmetric scaffolds was envisioned to give test compounds of type **4**, **5** and **6** with chirality resulting from stereogenic centers only.

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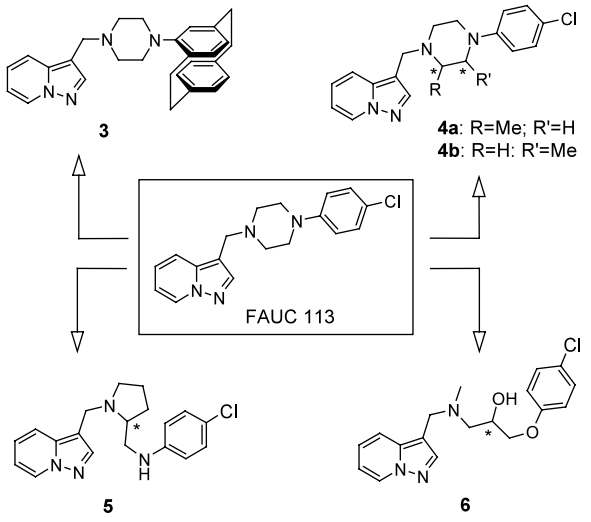
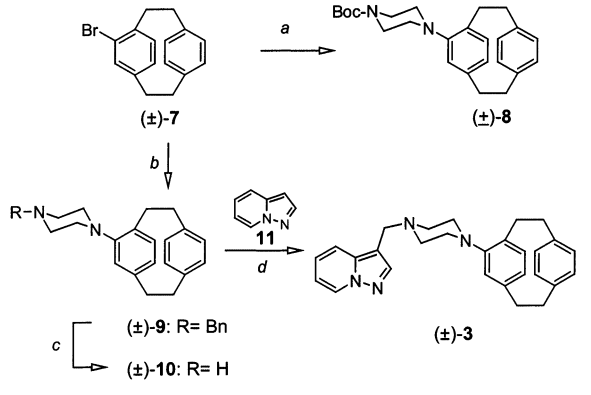


Figure 2. Analogs of FAUC 113 with central- and planar-chirality.

2. Chemistry

When benzylamine was employed as the nucleophile, amination of dibromo[2.2]paracyclophane could be accomplished by palladium-catalyzed coupling reaction.[10] Further amination reactions of [2.2]paracyclophanyl bromides have not been described in the literature, yet. Our attempts to use $Pd_2dba_3/P(tBu)_3$ as a catalyst system for coupling of *N*-Boc protected piperazine to racemic 4-bromo[2.2]paracyclophane **7** failed, when only traces of the amination product (±)-**8** were obtained (Scheme 1).

Employing a palladium free, KO*t*Bu-catalyzed procedure,[11] the cyclophanylpiperazine (±)-**8** could be isolated in 16% yield. Under the same reaction conditions *N*-benzylpiperazine could be efficiently transformed into the corresponding cyclophanyl derivative (±)-**9** (64%). Surprisingly, the benzyl protecting group of (±)-**9** could not be removed using standard conditions



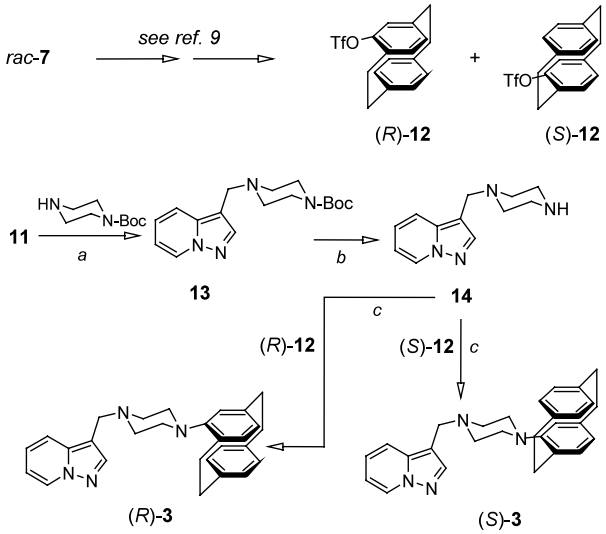
Scheme 1. *Reagents and conditions*: (a) *N*-Boc-piperazine, KO*t*Bu, toluene, 130°C, 48 h (16%); (b) *N*-benzylpiperazine, KO*t*Bu, toluene, 130°C, 24 h (64%); (c) 1. $ClCO_2Me$, reflux, 3 h; 2. conc. HCl, reflux, 16 h (65%); (d) CH_2O, HOAc, DCM, rt, 16 h (81%).

(H_2, Pd/C). The cleavage was successful when following the methodology described by Kanth and co-workers.[12] Here, the benzylpiperazine was transformed into a carbamate by treatment with methyl chloroformate followed by acid catalyzed release of the secondary amine (±)-**10**. Subsequent Mannich reaction of the cyclophanylpiperazine with pyrazolo[1,5-*a*]pyridine **11** gave the desired compound (±)-**3** possessing only planar-chirality.

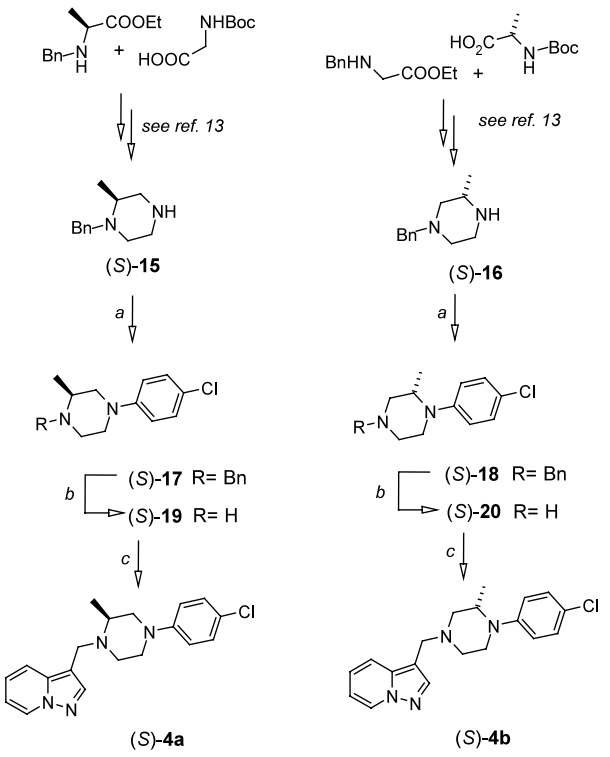
Due to the predicted formation of achiral aryne-type intermediates, the aforementioned base-catalyzed amination reaction was not suitable for the preparation of enantiopure piperazinyl cyclophanes (*R*)-**3** and (*S*)-**3**. Thus, we took advantage of our recently reported amination sequence employing the cyclophanyl triflates (*R*)-**12** and (*S*)-**12** as key intermediates, which can be approached by kinetic resolution of 4-acetoxy[2.2]paracyclophane with lipase from *Candida cylindracea* and subsequent sulfonylation[9] (Scheme 2).

We next tried to elaborate the palladium-promoted amination. We succeeded when the triflates (*R*)-**12** and (*S*)-**12** were treated with piperazinylmethyl substituted pyrazolo[1,5-*a*]pyridine **14**, which was obtained by carbamate cleavage of the Mannich base **13**, in the presence of Pd_2dba_3 and dppf. Under these conditions, the desired stereoisomers (*R*)-**3** and (*S*)-**3** could be isolated in 42% yield from (*R*)-**12** and (*S*)-**12**, respectively.

The synthesis of the methyl substituted derivatives of FAUC 113 started from the enantiopure *N*-benzylmethylpiperazines (*S*)-**15** and (*S*)-**16**, which were synthesized from suitably protected alanine and glycine precursors according to an ex-chiral pool procedure reported by Kiely and co-workers[13] (Scheme 3). Palladium-catalyzed arylation with 1-bromo-4-chlorobenzene furnished the 4-chlorophenyl piperazines (*S*)-**17** and (*S*)-**18** in 74 and 67% yield, respectively. After



Scheme 2. *Reagents and conditions*: (a) CH_2O, HOAc, DCM, rt, 3 days (80%); (b) 4N HCl, dioxane, 0°C, 20 min. (90%); (c) Pd_2dba_3, dppf, NaO*t*Bu, toluene, 100°C, 24 h (42%).

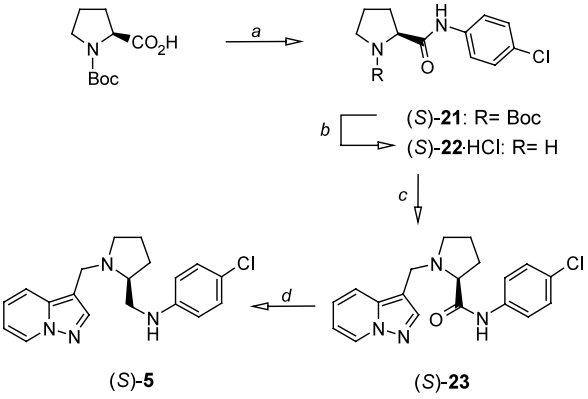


Scheme 3. *Reagents and conditions*: (a) 1-Bromo-4-chlorobenzene $Pd_2(dba)_3$, $P(tBu)_3$, $NaOtBu$, toluene, 120°C, 5 h (74% for **17**, 67% for **18**); (b) 1. $ClCO_2Me$, rt, 1.5 h; 2. KOH, MeOH, reflux, 72 h (81% for **19**, 70% for **20**); (c) **11**, CH_2O, HOAc, CH_2Cl_2, rt, 16 h (71% for **4a**, 81% for **4b**).

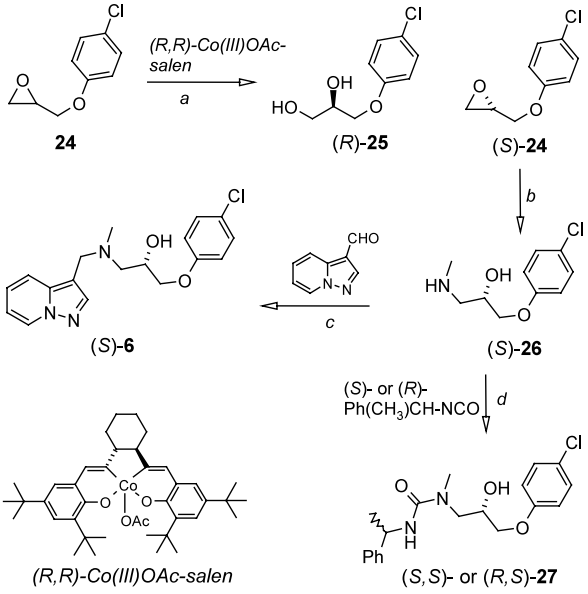
cleavage of the benzyl protecting groups the corresponding secondary amines (*S*)-**19** and (*S*)-**20** were converted into the respective pyrazolo[1,5-*a*]pyridines (*S*)-**4a** and (*S*)-**4b**. The enantiomers (*R*)-**4a** and (*R*)-**4b** were prepared analogously starting from the respective methylpiperazines (*R*)-**15** and (*R*)-**16**.

The synthesis of the enantiopure 2-aminomethyl pyrrolidine framework, which was selected to serve as an alternative diamine surrogate, started from Boc protected L-proline. DCC-mediated coupling with 4-chloroaniline furnished the proline amide (*S*)-**21** (Scheme 4). After cleavage of the protecting group, the resulting secondary amine (*S*)-**22** was transformed into the pyrazolo[1,5-*a*]pyridine derivative (*S*)-**23** using Mannich conditions. Finally, reduction with $LiAlH_4$ gave the desired test compound (*S*)-**5** in 43% overall yield. The enantiomer (*R*)-**5** was prepared analogously starting from Boc-D-proline.

The enantiopure amino alcohol **6** was synthesized starting from 4-chlorophenyloxymethyl oxirane **24**. Applying Jacobsen's hydrolytic kinetic resolution (HKR)[14] methodology, ring-opening of the epoxide **24**[15] with 0.5 equiv. of H_2O mediated by (*R*,*R*)-Co(III)-salen gave the diol (*R*)-**25** besides unreacted (*S*)-**24**, which was treated with methylamine to obtain the 1,2-aminoalcohol (*S*)-**26**. Finally, reductive alkylation with pyrazolo[1,5-*a*]-pyridine-3-carbaldehyde[16] gave the test compound (*S*)-**6**



Scheme 4. *Reagents and conditions*: (a) 4-chloroaniline, DCC, HOBt, EtOAc, rt, 17 h (82%); (b) HCl, EtOAc, rt, 16 h (97%); (c) **11**, CH_2O, Et_2MeN, HOAc, CH_2Cl_2, rt, 16 h (88%); (d) $LiAlH_4$, THF, 0°C–rt, 4 h (62%).



Scheme 5. *Reagents and conditions*: (a) H_2O, 0°C–rt, 2 h (44% of (*S*)-**24**); (b) $MeNH_2$ (33% in EtOH), rt, 2 h (94%); (c) $Na(OAc)_3BH$, CH_2Cl_2, rt, 16 h (89%); (d) THF, 0°C–rt, 3 h (89% for (*S*,*S*)-**27**, 89% for (*R*,*S*)-**27**).

(Scheme 5). The enantiomeric integrity of the synthesis was established by derivatization of (*S*)-**26**. Thus, coupling of the secondary amine with (*R*)- or (*S*)-phenylethylisocyanate gave the ureas (*R*,*S*)-**27** or (*S*,*S*)-**27**, respectively. ^1H NMR spectra proved the synthetic material to be enantiomerically pure. The enantiomer (*R*)-**6** was prepared analogously employing (*S*,*S*)-Co(III)-salen as a catalyst.

3. Pharmacology

Both enantiomers of the test compounds **3**, **4a**, **4b**, **5** and **6** were evaluated in vitro for their ability to displace [^3H]spiperone from the cloned human dopamine receptors $D2_{long}$, $D2_{short}$,[17] D3[18] and D4[19] being stably expressed in CHO cells. D1 affinity was determined by

employing bovine striatal membrane preparations and the D1 selective antagonist [^{3}H]SCH 23390.[20]

The dopamine receptor binding profiles of the double-layered test compounds (*R*)-**3** and (*S*)-**3** clearly indicate a significant loss of D4 affinity when compared to FAUC 113 (Table 1). On the other hand, ligand recognition at the D2 and D3 subtypes increased 18- to 90-fold. The central chiral FAUC 113 analogs (*R*)-**4a** and (*R*)-**4b** revealed K_i values at the D4 receptor in low nanomolar range, when selectivity over $D2_{long}$ and $D2_{short}$ was significantly enhanced in the case of (*R*)-**4a**. Irrespective of the absolute configuration, displacement of the piperazine moiety by aminomethylpyrrolidine or a vicinal amino alcohol group resulting in the test compounds **5** and **6**, respectively, was not tolerated by the D4 receptor.

Table 1. Dopamine receptor binding (K_i values [nM]) of the pyrazolo[1,5-*a*]pyridines (*R*)-**3**, (*S*)-**3**, (*R*)-**4a**,**b**, (*S*)-**4a**,**b**, (*R*)-**5**, (*S*)-**5**, (*R*)-**6** and (*S*)-**6** compared to the lead structure FAUC 113[a]

Compd	D1	$D2_{long}$	$D2_{short}$	D3	D4
(*R*)-**3**	5500	170	130	87	117
(*S*)-**3**	3400	100	84	55	100
(*S*)-**4a**	1200	12000	6500	6100	47
(*R*)-**4a**	1700	40000	20000	11000	6.2
(*S*)-**4b**	7700	4900	4500	13000	30
(*R*)-**4b**	9100	6800	10000	5700	3.9
(*R*)-**5**	7300	19000	18000	4500	2100
(*S*)-**5**	22000	19000	23000	4700	1800
(*R*)-**6**	6700	53000	43000	9900	970
(*S*)-**6**	13000	24000	11000	14000	1300
FAUC 113	12000	3200	4300	5000	3.1

[a] Data are based on the means of 2–3 experiments performed in triplicate at eight concentrations.

4. Conclusion

In conclusion, we have synthesized a number of enantiomerically pure FAUC 113 analogs featuring central- or planar-chiral information. Radioligand binding studies demonstrated, that the affinity to the dopamine D2 and D3 receptor subtypes could be enhanced when the chlorophenyl moiety is replaced by a [2.2]paracyclophane group. Depending on the absolute configuration, the incorporation of a stereogenic center into the piperazine substructure significantly influenced the D4 selectivity.

5. Experimental

5.1. General procedures

Melting points were determined on a Büchi 530 apparatus and are uncorrected. All ^{1}H And ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solution with Bruker AC spectrometers at 360 MHz as well as 90 and 63 MHz. Elemental analyses were performed by the Department of Organic Chemistry, University of Erlangen-Nürnberg. Optical rotations were measured with a Perkin–Elmer 241 spectropolarimeter. THF and toluene were freshly distilled from sodium benzophenone or sodium, respectively. All reagents were of commercial quality and used as purchased. Flash chromatography was carried out with silica gel 60 (4.0–6.3 μm) eluting with appropriate solution in the stated v:v proportions. Analytical thin-layer chromatography (TLC) was performed with silica gel plates on aluminium (silica gel 60 F_{254} from Merck).

5.2. 1-*tert*-Butyloxycarbonyl-4-[2.2]paracyclophan-4-ylpiperazine, (±)-8

A suspension of (±)-**7** (50 mg, 0.175 mmol), *N*-Boc-piperazine (110 mg, 0.59 mmol) and KO*t*Bu (66 mg, 0.59 mmol) and toluene (1 mL) was stirred in a sealed tube at 130°C for 48 h. Saturated aqueous $NaHCO_3$ solution was added and the aqueous layer was extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and evaporated and the residue was purified by flash chromatography (petroleum ether–EtOAc 4:1) to afford (±)-**8** as a colorless solid (36 mg, 16%): IR (KBr): ν 2925, 2852, 1697, 1415, 1170 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.49 (s, 9H), 2.71 (ddd, 1H, J=13.1, 10.0, 6.4 Hz), 2.80–3.74 (m, 15H), 5.72 (d, 1H, J=1.7 Hz), 6.30 (dd, 1H, J=7.5, 1.8 Hz), 6.36 (dd, 1H, J=7.8, 1.8 Hz), 6.43 (d, 1H, J=7.5 Hz), 6.45 (dd, 1H, J=7.8, 1.8 Hz), 6.53 (dd, 1H, J=7.8, 1.7 Hz), 6.67 (dd, 1H, J=7.8, 1.8 Hz).

5.3. 1-Benzyl-4-[2.2]paracyclophan-4-ylpiperazine, (±)-9

A suspension of (±)-**7** (200 mg, 0.699 mmol), *N*-benzylpiperazine (176 mg, 1.00 mmol) and KO*t*Bu (156 mg, 1.39 mmol) and toluene (2 mL) was stirred in a sealed tube at 130°C for 24 h. Then, a saturated solution of $NaHCO_3$ was added and the aqueous layer was extracted with Et_2O. The combined organic layers were dried ($NaSO_4$) and evaporated and the residue was purified by flash chromatography (petroleum ether–EtOAc 4:1) to afford (±)-**9** as a colorless solid (171 mg, 64%): mp 134°C; IR (KBr): ν 2925, 2810, 1587, 1490, 1231, 737 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$): δ 2.59–2.75 (m, 4H), 2.87–3.07 (m, 10H), 3.26 (ddd, 1H, J=12.5, 9.3, 6.3 Hz), 3.37 (ddd, 1H, J=12.9, 9.4, 2.2 Hz), 3.59 (d, 1H, J=12.9 Hz), 3.63 (d, 1H, J=12.9 Hz), 5.70 (d, 1H, J=1.4 Hz), 6.26 (dd, 1H, J=7.6, 1.4 Hz), 6.34 (dd, 1H, J=7.8, 1.8 Hz), 6.39 (d, 1H, J=7.6 Hz), 6.44 (dd, 1H, J=7.8, 1.8, Hz), 6.52 (d, 1H, J=7.9 Hz), 6.69 (dd, 1H, J=7.9, 1.8 Hz), 7.23–7.40 (m, 5H); MS m/z=382 [M$^+$]. Anal. calcd for $C_{27}H_{30}N_2$: C, 84.77; H, 7.90; N, 7.32. Found: C, 84.35; H, 7.94; N, 6.89%.

5.4. *N*-[2.2]Paracyclophan-4-ylpiperazine, (±)-10

A mixture of (±)-**9** (50 mg, 0.131 mmol) and $ClCO_2CH_3$ (2 mL) was heated under reflux for 3 h. After removal of the formic ester the residue was dissolved in conc HCl (2 mL) and refluxed for 16 h. Then careful alkalization with 2N NaOH and extraction with EtOAc the combined organic layers were dried (Na_2SO_4) and evap-

orated. The residue was purified by flash chromatography (CH_2Cl_2–MeOH–$EtMe_2N$ 9:1:0.1) to afford (±)-**10** amine as a colorless solid (25 mg, 65%): mp >200°C decomposition; IR (KBr): ν 3433, 2928, 2722, 1590, 1412, 742 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$): δ 2.76 (ddd, 1H, $J=13.1$, 9.9, 6.2 Hz), 2.86 (s, 1H), 2.91–3.53 (m, 15H), 5.84 (d, 1H, $J=1.7$ Hz), 6.36 (dd, 1H, $J=7.6$, 1.7 Hz), 6.42 (dd, 1H, $J=7.8$, 1.7 Hz), 6.46 (dd, 1H, $J=7.8$, 1.7 Hz), 6.47 (d, 1H, $J=7.8$ Hz), 6.53 (dd, 1H, $J=7.8$, 1.7 Hz), 6.68 (dd, 1H, $J=7.6$, 1.7 Hz); MS $m/z=292$ [M^+]. Anal. calcd for $C_{20}H_{24}N_2$: C, 82.15; H, 8.27; N, 9.58. Found: C, 82.41; H, 7.94; N, 9.87%.

5.5. 4-(Pyrazolo[1,5-*a*]pyridin-3-ylmethyl)piperazinyl-1-carboxylic acid *tert*-butyl ester, 13

A solution of pyrazolo[1,5-*a*]pyridine **11** (100 mg, 0.847 mmol), CH_2O (68 μL of a 37% solution, 0.839 mmol), *tert*-butyl piperazine-1-carboxylate (150 mg, 0.847 mmol) and HOAc (three drops) was stirred in CH_2Cl_2 (6 mL) at room temperature for 3 days. Saturated aqueous $NaHCO_3$ solution was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated and the residue was purified by flash chromatography (EtOAc–MeOH 95:5) to afford **13** as a colorless solid (202 mg, 80%): mp 116°C; IR (KBr): ν 2976, 2861, 1681, 1426, 1240, 1126, 760 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.34–2.49 (m, 4H), 3.35–3.48 (m, 4H), 3.70 (s, 2H), 6.74 (ddd, 1H, $J=7.0$, 6.5, 1.0 Hz), 7.09 (ddd, 1H, $J=9.2$, 6.5, 0.8 Hz), 7.59 (ddd, 1H, $J=9.2$, 1.0, 0.8, Hz), 7.87 (s, 1H), 8.43 (ddd, 1H, $J=7.0$, 0.8, 0.8 Hz); MS $m/z=316$ [M^+]. Anal. calcd for $C_{17}H_{24}N_4O_2$: C, 64.53; H, 7.65; N, 17.71. Found: C, 64.89; H, 7.81; N, 18.20%.

5.6. *N*-Pyrazolo[1,5-*a*]pyridin-3-ylmethylpiperazine, 14

A mixture of **13** (182 mg, 0.607 mmol) was stirred in a HCl solution (4N in dioxane) at 0°C for 20 min. Then, the solvent was evaporated and the hydrochloride was obtained. The residue was resolved in 2N NaOH and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated to give **14** as a colorless solid (110 mg, 90%): mp 61°C; IR (KBr): ν 3854, 2923, 2819, 1635, 1471, 1129, 742 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$): δ 2.49 (br s, 4H), 2.76–2.87 (m, 4H), 3.73 (s, 2H), 4.85 (s, 1H), 6.88 (ddd, 1H, $J=7.0$, 6.8, 1.0 Hz), 7.23 (ddd, 1H, $J=9.0$, 6.8, 1.0 Hz), 7.72 (ddd, 1H, $J=9.0$, 1.0, 1.0, Hz), 7.92 (s, 1H), 8.48 (ddd, 1H, $J=7.0$, 1.0, 1.0 Hz); MS $m/z=216$ [M^+]. Anal. calcd for $C_{12}H_{16}N_4$: C, 66.64; H, 7.46; N, 25.90. Found: C, 66.94; H, 7.41; N, 25.69%.

5.7. (*R*)-3-(4-[2.2]Paracyclophan-4-ylpiperazin-1-ylmethyl)pyrazolo[1,5-*a*]pyridine, (*R*)-3

A solution of (*R*)-**12** (7 mg, 0.019 mmol), **14** (4.2 mg, 0.019 mmol), NaO*t*Bu (2.7 mg, 0.022 mmol), $Pd_2(dba)_3$ (0.5 mg, 0.55 μmol) and dppf (1.1 mg, 1.99 μmol) in toluene (0.5 mL) was stirred at 100°C for 24 h. After cooling to rt Et_2O was added and extracted with saturated $NaHCO_3$ solution. The aqueous layer was washed with ether several times. The combined organic layers were dried (Na_2SO_4) and evaporated and the residue was purified by flash chromatography (EtOAc) to afford (*R*)-**3** as a colorless solid (3.5 mg, 42%): mp 130°C; IR (KBr): ν 2924, 2812, 1634, 1586, 1415, 730 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$): δ 2.60–2.80 (m, 5H), 2.84–3.10 (m, 9H), 3.24 (ddd, 1H, $J=12.7$, 9.3, 6.2 Hz), 3.36 (ddd, 1H, $J=12.8$, 9.5, 2.3 Hz), 3.80 (s, 2H), 5.70 (d, 1H, $J=1.7$ Hz), 6.26 (dd, 1H, $J=7.5$, 1.7 Hz), 6.34 (dd, 1H, $J=7.7$, 1.7 Hz), 6.39 (d, 1H, $J=7.5$ Hz), 6.47 (dd, 1H, $J=7.7$, 1.7 Hz), 6.52 (dd, 1H, $J=7.7$, 1.7 Hz), 6.68 (dd, 1H, $J=7.7$, 1.7 Hz), 6.76 (ddd, 1H, $J=6.7$, 6.7, 1.0 Hz), 7.12 (ddd, 1H, $J=8.7$, 6.7, 1.0 Hz), 7.66 (ddd, 1H, $J=8.7$, 1.0, 1.0 Hz), 7.94 (s, 1H), 8.46 (ddd, 1H, $J=6.7$, 1.0, 1.0 Hz); MS $m/z=422$ [M^+]. Anal. calcd for $C_{28}H_{30}N_4$: C, 79.59; H, 7.16; N, 13.26. Found: C, 79.45; H, 7.19; N, 13.19%. $[\alpha]_D^{20}=+11.4$ (c 0.5, $CHCl_3$). Starting from (*S*)-**12** and **14**, (*S*)-**3** was prepared under identical conditions $[\alpha]_D^{20}=-10.4$ (c 0.5, $CHCl_3$); HPLC: Chiralcel OD column, solvent (petroleum ether–*i*PrOH 6:4), $P=28$ bar, flowrate = 1.0 ml/min; R_t ((*R*)-**3**) = 21.1 min, R_t ((*S*)-**3**) = 17.8 min; [e.e.]: (*R*)-**3** >98%; (*S*)-**3** >98%.

5.8. (*S*)-1-Benzyl-4-(4-chlorophenyl)-2-methylpiperazine, (*S*)-17

A mixture of (*S*)-**15** (47.3 mg, 0.247 mmol), *p*-bromochlorobenzene (70 mg, 0.365 mmol), NaO*t*Bu (35 mg, 0.365 mmol) and $Pd_2(dba)_3$ (1.2 mg, 1.31 μmol) was treated with a freshly prepared solution of $P(tBu)_3$ 0.021 mmol/l in toluene, 0.5 ml) under a nitrogen atmosphere and heated in a sealed tube for 5 h at 120°C. After cooling to room temperature EtOAc was added and the mixture was washed with saturated $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and evaporated and the residue was purified by flash chromatography (petroleum ether–EtOAc 9:1) to afford (*S*)-**17** as a colorless solid: mp 78°C; ^1H NMR (360 MHz, $CDCl_3$): δ 1.23 (d, 3H, $J=5.9$ Hz), 2.29 (ddd, 1H, $J=11.5$, 11.0, 3.3 Hz), 2.61 (ddd, 1H, $J=9.0$, 5.9, 2.8 Hz), 2.68 (dd, 1H, $J=10.9$, 9.0 Hz), 2.81 (ddd, 1H, $J=11.5$, 3.6, 3.3 Hz), 2.84 (ddd, 1H, $J=11.5$, 11.0, 3.3 Hz), 3.20 (d, 1H, $J=13.0$ Hz), 3.31 (dddd, 1H, $J=11.5$, 3.6, 3.3, 1.5 Hz), 3.38 (ddd, 1H, $J=10.9$, 2.8, 1.5 Hz), 4.10 (d, 1H, $J=13.0$ Hz), 6.78–6.84 (m, 2H), 7.15–7.21 (m, 2H), 7.23–7.37 (m, 5H); MS $m/z=300$ [M^+]. Anal. calcd for $C_{18}H_{21}ClN_2$: C, 71.87; H, 7.04; N, 9.31. Found: C, 72.05; H, 7.14; N, 9.26%. $[\alpha]_D^{20}=+62.8$ (c 1, $CHCl_3$). Starting from (*R*)-**15**, (*R*)-**17** was prepared under identical conditions $[\alpha]_D^{20}=-63.4$ (c 1, $CHCl_3$).

5.9. (*S*)-4-Benzyl-1-(4-chlorophenyl)-2-methylpiperazine, (*S*)-18

Starting from (*S*)-**16** (102 mg, 0.537 mmol), (*S*)-**18** was prepared in 67% yield following the procedure described for (*S*)-**17** (Section 5.8): mp 109°C; ^1H NMR (360 MHz, $CDCl_3$): δ 1.06 (d, 3H, $J=6.3$ Hz), 2.34 (ddd, 1H, $J=10.6$, 9.9, 3.9 Hz), 2.46 (dd, 1H, $J=11.0$, 3.4 Hz), 2.60 (ddd, 1H, $J=11.0$, 3.5, 1.9 Hz), 2.82

(dddd, 1H, $J=10.6$, 3.7, 3.4, 1.9 Hz), 3.10 (ddd, 1H, $J=11.8$, 9.9, 3.4 Hz), 3.16 (ddd, 1H, $J=11.8$, 3.9, 3.7 Hz), 3.47 (d, 1H, $J=13.2$ Hz), 3.58 (d, 1H, $J=13.2$ Hz), 3.80 (ddd, 1H, $J=6.3$, 3.5, 3.4 Hz), 6.78–6.84 (m, 2H), 7.16–7.21 (m, 2H), 7.23–7.29 (m, 1H), 7.30–7.39 (m, 4H); MS $m/z=300$ [M$^+$]. Anal. calcd for $C_{18}H_{21}ClN_2$: C, 71.87; H, 7.04; N, 9.31. Found: C, 71.71; H, 6.89; N, 9.12%. $[\alpha]_D^{20}=-23.1$ (c 1, $CHCl_3$). Starting from (*R*)-**16**, (*R*)-**18** was prepared under identical conditions $[\alpha]_D^{20}=+22.4$ (c 1, $CHCl_3$).

5.10. (*S*)-1-(4-Chlorophenyl)-3-methylpiperazine, (*S*)-19

A solution of (*S*)-**17** (32 mg, 0.106 mmol) in methyl chloroformate (1.0 ml) was stirred for 1.5 h at room temperature. The mixture was evaporated and the residue was treated with two pearls of KOH and MeOH (2 ml). After refluxing for 3 days, the solvent was evaporated. Addition of a saturated solution of $NaHCO_3$, extraction with $CHCl_3$ and evaporation of the dried (Na_2SO_4) organic layer gave the crude product, which was purified by flash chromatography (CH_2Cl_2–MeOH–$EtMe_2N$ 9:1:0.1) to give (*S*)-**19** (18.1 mg, 81%) as a colorless solid: mp 67°C; IR (KBr): ν 3256; ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.13 (d, 3H, $J=6.2$ Hz), 1.54 (s, 1H), 2.33 (dd, 1H, $J=11.7$, 10.0 Hz), 2.68 (ddd, 1H, $J=11.6$, 11.6, 3.3 Hz), 2.97 (ddd, 1H, $J=10.0$, 6.4, 3.3 Hz), 3.02 (ddd, 1H, $J=11.7$, 11.6, 3.1 Hz), 3.11 (ddd, 1H, $J=11.7$, 3.3, 2.3 Hz), 3.43–3.49 (m, 2H), 6.81–6.87 (m, 2H), 7.17–7.22 (m, 2H); MS $m/z=210$ [M$^+$]. Anal. calcd for $C_{11}H_{15}ClN_2$: C, 62.70; H, 7.18; N, 13.29. Found: C, 63.20; H, 7.39; N, 13.47%. $[\alpha]_D^{20}=-4.3$ (c 1, $CHCl_3$). Starting from (*R*)-**17**, (*R*)-**19** was prepared under identical conditions $[\alpha]_D^{20}=+4.3$ (c 1, $CHCl_3$).

5.11. (*S*)-1-(4-Chlorophenyl)-2-methylpiperazine, (*S*)-20

Starting from (*S*)-**18** (50.5 mg, 0.168 mmol), (*S*)-**20** was prepared in 70% yield following the procedure described for (*S*)-**19** (Section 5.10): mp 54°C; ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.02 (d, 3H, $J=6.5$ Hz), 1.78 (s, 1H), 2.85 (ddd, 1H, $J=12.1$, 3.3, 0.7 Hz), 2.89–3.20 (m, 5H), 3.70 (ddd, 1H, $J=6.5$, 3.3, 3.3 Hz), 6.77–6.91 (m, 2H), 7.13–7.28 (m, 2H); MS $m/z=210$ [M$^+$]. Anal. calcd for $C_{11}H_{15}ClN_2$: C, 62.70; H, 7.18; N, 13.29. Found: C, 62.39; H, 7.30; N, 13.13%. $[\alpha]_D^{20}=-32.0$ (c 1, $CHCl_3$). Starting from (*R*)-**18**, (*R*)-**20** was prepared under identical conditions $[\alpha]_D^{20}=+32.2$ (c 1, $CHCl_3$).

5.12. (*S*)-3-[4-(4-Chlorophenyl)-2-methylpiperazin-1-ylmethyl]pyrazolo[1,5-*a*]pyridine, (*S*)-4a

A mixture of (*S*)-**19** (10 mg, 0.048 mmol), **11** (11.2 mg, 0.095 mmol), formaldehyde (7.7 μl, 37% in H_2O, 0.095 mmol) and HOAc (three drops) in CH_2Cl_2 (1.5 ml) was stirred for 16 h at room temperature. After addition of a saturated solution of $NaHCO_3$ the organic layer was separated, dried (Na_2SO_4) and evaporated. The crude product was purified by flash chromatography (EtOAc) to give (*S*)-**4a** (11.4 mg, 71%) as a colorless solid: mp 110°C; IR (KBr): ν 1634 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.31 (d, 3H, $J=5.8$ Hz), 2.33 (ddd, 1 H, $J=11.5$, 11.2, 3.2 Hz), 2.60 (ddd, 1H, 10.0, 5.8, 3.4 Hz), 2.67 (dd, 1H, $J=10.6$, 10.0 Hz), 2.82 (ddd, 1H, $J=11.6$, 11.2, 3.4 Hz), 2.87 (ddd, 1H, $J=11.5$, 3.5, 3.4 Hz), 3.32 (dddd, 1H, $J=11.6$, 3.5, 3.2, 1.8 Hz), 3.39 (ddd, 1H, $J=10.6$, 3.4, 1.8 Hz), 3.56 (d, 1H, $J=13.7$ Hz), 4.21 (d, 1H, $J=13.7$ Hz), 6.75 (ddd, 1H, $J=6.9$, 6.9, 1.2 Hz), 6.77–6.82 (m, 2H), 7.09 (ddd, 1H, $J=8.9$, 6.9, 1.1 Hz), 7.14–7.20 (m, 2H), 7.63 (ddd, 1H, $J=8.9$, 1.2, 1.1 Hz), 7.90 (s, 1H), 8.44 (ddd, 1H, $J=6.9$, 1.1, 1.1 Hz); MS $m/z=340$ [M$^+$]. Anal. calcd for $C_{19}H_{21}ClN_4$: C, 66.95; H, 6.21; N, 16.44. Found: C, 67.30; H, 6.28; N, 16.53%. $[\alpha]_D^{20}=+75.6$ (c=1, $CHCl_3$). Starting from (*R*)-**19**, (*R*)-**4a** was prepared under identical conditions $[\alpha]_D^{20}=-76.0$ (c 1, $CHCl_3$).

5.13. (*S*)-3-[4-(4-Chlorophenyl)-3-methylpiperazin-1-ylmethyl]pyrazolo[1,5-*a*]pyridine (*S*)-4b

Starting from (*S*)-**20** (11.5 mg, 0.055 mmol), (*S*)-**4b** was prepared in 81% yield following the procedure described for (*S*)-**4a** (Section 5.12): mp 137°C; IR (KBr): ν 1634 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.03 (d, 3H, $J=6.5$ Hz), 2.33 (ddd, 1 H, $J=10.5$ 10.0, 3.6 Hz), 2.47 (dd, 1H, $J=10.9$, 3.3 Hz), 2.63 (ddd, 1H, $J=10.9$, 3.4, 1.7 Hz), 2.84 (dddd, 1H, $J=10.5$, 3.6, 3.3, 1.7 Hz), 3.07 (ddd, 1H, $J=11.9$, 10.0, 3.3 Hz), 3.15 (ddd, 1H, $J=11.9$, 3.6, 3.6 Hz), 3.67 (d, 1H, $J=13.4$ Hz), 3.74 (d, 1H, $J=13.4$ Hz), 3.80 (ddd, 1H, $J=6.5$, 3.4, 3.3 Hz), 6.75 (ddd, 1H, $J=6.7$, 6.7, 1.0 Hz), 6.77–6.83 (m, 2H), 7.09 (ddd, 1H, $J=8.8$, 6.7, 1.0 Hz), 7.15–7.21 (m, 2H), 7.65 (ddd, 1H, $J=8.8$, 1.0, 0.9 Hz), 7.89 (s, 1H), 8.44 (ddd, 1H, $J=6.7$, 1.0, 0.9 Hz); MS $m/z=340$ [M$^+$]; $[\alpha]_D^{20}=-21.6$ (c 1, $CHCl_3$). Starting from (*R*)-**20**, (*R*)-**4b** was prepared under identical conditions $[\alpha]_D^{20}=+21.0$ (c 1, $CHCl_3$).

5.14. *N*-Boc-L-proline-4-chlorophenylamide, (*S*)-21

A mixture of *N*-Boc-L-proline (1.00 g, 4.65 mmol), DCC (1.15 g, 5.58 mmol) and HOBt (0.75 g, 5.58 mmol) in EtOAc (10 ml) was stirred at room temperature for 1 h. After addition of 4-chloroaniline (0.85 g, 5.56 mmol), stirring was continued for 16 h followed by addition of EtOAc (10 ml) and $CHCl_3$ (10 ml). The *N*,*N*′-dicyclohexylurea was separated by filtration and the clear solution was evaporated. Purification by flash chromatography (petroleum ether–EtOAc 3:7) afforded (*S*)-**21** as a colorless solid (0.87 g, 82%): mp 168°C; IR (KBr): ν 3290, 1702, 1669 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.48 (s, 9H), 1.57–1.69 (m, 1H), 1.88–1.99 (m, 2H), 2.45–2.62 (m, 1H), 3.30–3.51 (m, 2H), 4.40–4.49 (m, 1H), 7.22–7.30 (m, 2H), 7.44–7.99 (m, 2H), 9.60 (br s, 1H); MS m/z 324 [M$^+$]; $[\alpha]_D^{20}=-92.3$ (c 1, $CHCl_3$). Starting from *N*-Boc-D-proline, (*R*)-**21** was prepared under identical conditions $[\alpha]_D^{20}=+90.7$ (c 1, $CHCl_3$).

5.15. L-Proline-4-chlorophenylamide hydrochloride, (*S*)-22·HCl

A solution of (*S*)-**21** (900 mg, 2.77 mmol) in EtOAc (8 ml) was treated with a saturated solution of HCl in EtOAc (10 ml) and stirred for 16 h. Evaporation of the

solvent was followed by washing of the residue with Et_2O/EtOH (95/5) to give (*S*)-**22**·HCl (702 mg, 97%) as a colorless solid: mp 190°C; IR (KBr): *v* 3249, 3119, 1686, 1612 cm^{-1}; ^1H NMR (360 MHz, DMSO-d_6): δ 1.98–2.02 (m, 3H), 2.36–2.47 (m, 1H), 3.20–3.31 (m, 2H), 4.38–4.45 (m, 1H), 7.39–7.45 (m, 2H), 7.66–7.72 (m, 2H), 8.69 (br s, 1H), 10.01 (br s, 1H), 11.14 (br. S, 1H); MS $m/z=224$ [M^+−HCl]. Anal. calcd for $C_{11}H_{14}Cl_2N_2O{\cdot}0.1H_2O$: C, 50.25; H, 5.44; N, 10.65. Found: C, 50.29; H, 5.43; N, 10.77%. $[\alpha]_D^{20}=-33.0$ (*c* 1, $CHCl_3$). Starting from (*R*)-**21**, (*R*)-**22**·HCl was prepared under identical conditions $[\alpha]_D^{20}=+32.0$ (*c* 1, $CHCl_3$).

5.16. *N*-Pyrazolo[1,5-*a*]pyridin-3-ylmethyl-L-proline-4-chlorophenylamide, (*S*)-23

A solution of (*S*)-**22**·HCl (100 mg, 0.44 mmol), **11** (52 mg, 0.44 mmol) and $EtMe_2N$ (35 mg, 0.44 mmol) in CH_2Cl_2 (4 ml) was treated with HOAc (0.30 ml) and formaldehyde (37% in H_2O, 44 μl) and stirred for 16 h at room temperature. Addition of a saturated solution of $NaHCO_3$ (10 ml) was followed by extraction with $CHCl_3$. The organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography (EtOAc) to give (*S*)-**23** (139 mg, 88%) as a colorless solid: mp 101–102°C; IR (KBr): *v* 3269, 1684, 1513 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$): δ 1.69–1.88 (m, 2H), 1.95–2.04 (m, 1H), 2.21–2.33 (m, 1H), 2.58 (ddd, 1H, $J=10.0$, 10.0, 6.5 Hz), 3.18 (ddd, 1H, $J=9.0$, 7.0, 2.0 Hz), 3.34 (dd, 1H, $J=10.0$, 3.5 Hz), 3.85 (d, 1H, $J=13.5$ Hz), 4.05 (d, 1H, $J=13.5$ Hz), 6.75 (ddd, 1H, $J=7.0$, 7.0, 1.5 Hz), 7.12 (ddd, 1H, $J=9.0$, 6.0, 1.0 Hz), 7.22–7.27 (m, 2H), 7.38–7.44 (m, 2H), 7.50 (br d, 1H, $J=9.0$ Hz), 7.90 (s, 1H), 8.41 (br d, 1H, 7.0 Hz), 9.35 (br s, 1H); MS $m/z=354$ [M^+]; $[\alpha]_D^{20}=-92.0$ (*c* 1, $CHCl_3$). Starting from (*R*)-**22**·HCl, (*R*)-**23** was prepared under identical conditions $[\alpha]_D^{20}=+94.0$ (*c* 1, $CHCl_3$).

5.17. (*S*)-*N*-(4-Chlorophenyl)-*N*-(1-pyrazolo[1,5-*a*]-pyridin-3-ylmethylpyrrolidin-2-ylmethyl)amine, (*S*)-5

$LiAlH_4$ (1.0 M in THF, 0.270 ml) was added to a precooled (0°C) solution of (*S*)-**23** (90 mg, 0.25 mmol) in THF (5 ml). The mixture was warmed to room temperature and stirred for 4 h. Treatment with a saturated solution of $NaHCO_3$ was followed by extraction with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography (EtOAc) to give (*S*)-**5** (54 mg, 62%) as a colorless oil: IR (NaCl): *v* 3349, 2962, 2805, 1634, 1601, 1500 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$): δ 1.63–1.83 (m, 3H), 1.88–2.00 (m, 1H), 2.33 (q, 1H, $J=9.0$ Hz), 2.79–2.87 (m, 1H), 2.89–3.05 (m, 1H), 3.14–3.21 (m, 2H), 3.55 (d, 1H, $J=13.5$ Hz), 4.06 (d, 1H, $J=13.5$ Hz), 4.35 (br s, 1H), 6.48–6.53 (m, 2H), 6.73 (ddd, 1H, $J=7.0$, 7.0, 1.5 Hz), 7.05 (ddd, 1H, $J=9.0$, 6.0, 1.0 Hz), 7.09–7.14 (m, 2H), 7.46 (br d, 1H, $J=9.0$ Hz), 7.85 (s, 1H), 8.42 (br d, 1H, 7.0 Hz); MS $m/z=340$ [M^+]. Anal. calcd for $C_{19}H_{21}ClN_4$: C, 66.95; H, 6.21; N, 16.44. Found: C, 66.88; H, 6.20; N, 16.22%. $[\alpha]_D^{20}=-38.0$ (*c* 1, $CHCl_3$). Starting from (*R*)-**23**·HCl, (*R*)-**5** was prepared under identical conditions $[\alpha]_D^{20}=+37.0$ (*c* 1, $CHCl_3$).

5.18. (*S*)-2-(Chlorophenoxymethyl)oxirane, (*S*)-24

(*R*,*R*)-(salen)Co(III)OAc was prepared using the (*R*,*R*)-(salen)Co(II) precatalyst[21] (50 mg, 0.083 mmol), which was dissolved in CH_2Cl_2 (0.5 ml) and treated with HOAc (20 mg). After stirring for 10 min at room temperature, the solvent was evaporated to give a brown solid, which was used immediately without further purification. So, a mixture of **24**[15] (2.0 g, 10.8 mmol) and (*R*,*R*)-(salen)Co(III)OAc (37 mg, 0.057 mmol) was cooled to 0°C, treated with H_2O (0.110 ml, 6.1 mmol) and warmed to room temperature. The progress of the conversion was monitored by HPLC (RP18, MeOH/H_2O 1:1, UV 225 nm). After 2 h, the reaction was completed and the crude product was purified by flash chromatography (petroleum ether–EtOAc 2:3) to give (*S*)-**24** (0.88 mg, 44%) as a colorless oil: ^1H NMR (360 MHz, $CDCl_3$): δ 2.73 (dd, 1H, $J=4.5$, 2.5 Hz), 2.90 (t, 1H, 4.5 Hz), 3.31–3.37 (m, 1H), 3.91 (dd, 1H, $J=11.0$, 6.0 Hz), 4.21 (dd, 1H, $J=11.0$, 3.0 Hz), 6.81–6.88 (m, 2H), 7.21–7.27 (m, 2H); MS $m/z=184$ [M^+]; $[\alpha]_D^{20}=+3.2$ (*c* 1, $CHCl_3$). Starting from **24** and the (*S*,*S*)-(salen)Co(II) precatalyst,[21] (*R*)-**24** was prepared under identical conditions $[\alpha]_D^{20}=-3.2$ (*c* 1, $CHCl_3$).

5.19. (*S*)-1-(4-Chlorophenoxy)-3-methylaminopropan-2-ol, (*S*)-26

(*S*)-**24** (300 mg, 1.60 mmol) was treated with a solution of methylamine (33% in EtOH, 5 ml) and stirred for 2 h at room temperature. The solvent was evaporated and the residue was crystallized from Et_2O/EtOH to give (*S*)-**26** (0.33 g, 94%) as a colorless solid: mp 69°C; IR (KBr): *v* 3444, 3289, 2896, 2846, 1492 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$): δ 2.48 (s, 3H), 2.71–2.83 (m, 2H), 3.94–3.97 (m, 2H), 4.03–4.08 (m, 1H), 6.81–6.87 (m, 2H), 7.21–7.27 (m, 2H); MS $m/z=215$ [M^+]; $[\alpha]_D^{20}=-5.0$ (*c* 1, $CHCl_3$). Starting from (*R*)-**24**, (*R*)-**26** was prepared under identical conditions $[\alpha]_D^{20}=+6.2$ (*c* 1, $CHCl_3$).

5.20. Determination of the enantiomeric purity of (*S*)-26

(*S*)-Phenylethylisocyanate (8 mg, 0.054 mmol) was added at 0°C to a solution of (*S*)-**26** (10 mg, 0.047 mmol) in THF (1 ml). After stirring the mixture for 3 h, the solvent was evaporated and the unreacted starting material was separated by flash chromatography (petroleum ether–EtOAc 1:4) to give (*S*,*S*)-**27**. The coupling was also carried out with (*R*)-phenylethylisocyanate to give the appropriate diastereomer (*R*,*S*)-**27**. Diagnostic signals: ^1H NMR (360 MHz, $CDCl_3$) (*S*,*S*)-**27**: δ 3.48–3.60 (m, 2H); (*R*,*S*)-**27**: δ 3.55 (d, 2H, $J=4.5$ Hz).

5.21. (*S*)-1-(4-Chlorophenoxy)-3-(*N*-methyl-*N*-(pyrazolo[1,5-*a*]pyridin-3-ylmethyl)amino)propan-2-ol, (*S*)-6

A solution of (*S*)-**26** (80 mg, 0.37 mmol) and pyrazolo[1,5-*a*]pyridine-3-carbaldehyde[16] (60 mg, 0.41 mmol) in CH_2Cl_2 (5 ml) was treated with $Na(OAc)_3BH$ (87 mg, 0.41 mmol) and stirred for 16 h at room temperature. Addition of a saturated solution of $NaHCO_3$ was followed by extraction with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated and the crude product was purified by flash chromatography (EtOAc) to give (*S*)-**6** (115 mg, 89%) as a colorless solid: mp 63°C; IR (KBr): ν 3333, 2933, 2847, 1636, 1492, 1245, 747 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$): δ 2.31 (s, 3H), 2.54 (dd, 1H, $J=12.5$, 4.0 Hz), 2.66 (dd, 1H, $J=12.5$, 9.5 Hz), 3.76 (d, 1H, $J=13.5$ Hz), 3.88 (d, 1H, 13.5 Hz, $J=13.5$ Hz), 3.91 (d, 2H, $J=5.0$ Hz), 4.09–4.16 (m, 1H), 6.76 (ddd, 1H, $J=9.0$, 6.0, 1.0 Hz), 6.78–6.83 (m, 2H), 7.11 (ddd, 1H, $J=9.0$, 6.0, 1.0 Hz), 7.19–7.24 (m, 2H), 7.55 (br d, 1H, $J=9.0$ Hz), 7.88 (s, 1H), 8.44 (br d, 1H, $J=7.0$ Hz); MS $m/z=345$ [M^+]. Anal. calcd for $C_{18}H_{20}ClN_3O_2$: C, 62.52; H, 5.83; N, 12.15. Found: C, 62.48; H, 5.83; N, 12.13%. $[\alpha]_D^{20}=-26.0$ (*c* 0.5, $CHCl_3$). Starting from (*R*)-**26**, (*R*)-**6** was prepared under identical conditions $[\alpha]_D^{20}=+26.0$ (*c* 0.5, $CHCl_3$).

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