Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 60 (2004) 1197–1204
Tetrahedron

Practical ex-chiral-pool methodology for the synthesis of dopaminergic tetrahydroindoles

Markus Bergauer, Harald Hübner and Peter Gmeiner*

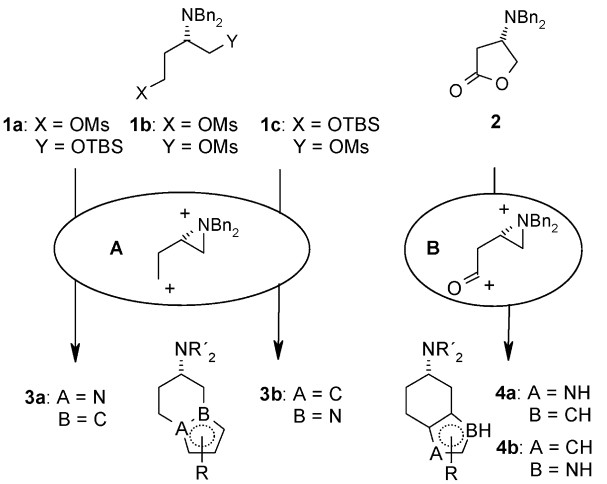
Department of Medicinal Chemistry, Emil Fischer Center, Friedrich Alexander University, Schuhstraße 19, D-91052 Erlangen, Germany

Received 10 September 2003; revised 13 November 2003; accepted 18 November 2003

Abstract—Chemo- and regioselective transformations of asparagine gave access to optically active 5- and 6-amino tetrahydroindolizines when the 3-aminobutyrolactone (*S*)-**2** was employed as a key intermediate. The target compounds were approached by a sequential and regiocontrolled bis-electrophilic attack in the positions 2 and 3 of the pyrrole ring system. Receptor binding experiments showed stereocontrolled receptor recognition leading to the D3 selective agonist (*S*)-**8** with D3 binding that is comparable to the natural neurotransmitter dopamine.

1. Introduction

Chemo- and regioselective functionalization of asparagine and aspartic acid has become an attractive method for the construction of bioactive compounds including natural products and non-proteinogenic amino acids.[1] We recently presented efficient methodology for a regioselective preparation of the aspartate derivatives **1a**–**c** disclosing a straightforward access to a variety of amino alcohols, β-amino acids and lactam-bridged peptide mimetics.[2] Depending on the chemical necessities, the introduction of nucleophiles can be realized in the positions 1, 2 and 4. Thus, the building blocks **1** can serve as equivalents for the chiral synthon **A**. Exploiting the 1,4-bis-electrophilic properties, valuable applications in the field of medicinal chemistry could be disclosed when the attack of pyrrole derived nucleophiles in the positions 1 and 2 of the heterocyclic unit led to slaframine derivatives and dopaminergic bicyclic ergoline analogs (**3a**,**b**).[3] As an extension of our very recent efforts,[4] target driven SAR studies required the access to regioisomeric azabicyclo[4.3.0]-nonanes of type **4** that should be approached by a sequential and regiocontrolled bis-electrophilic attack in the positions 2 and 3 of the pyrrole ring system. We envisioned realizing this plan by *C*-acylation and aziridinium promoted 6-*endo*-tet cyclization[5] when the dibenzyl-protected asparagine derivative (*S*)-**2**[6] should be employed as a synthetic equivalent for the synthon **B**. In this paper, we describe an enantiospecific approach of the 5- and 6-aminotetrahydroindoles **4a** and **4b**, and the regio- and stereoselective dopamine receptor binding of the test compounds in both enantiomeric configurations (Scheme 1).



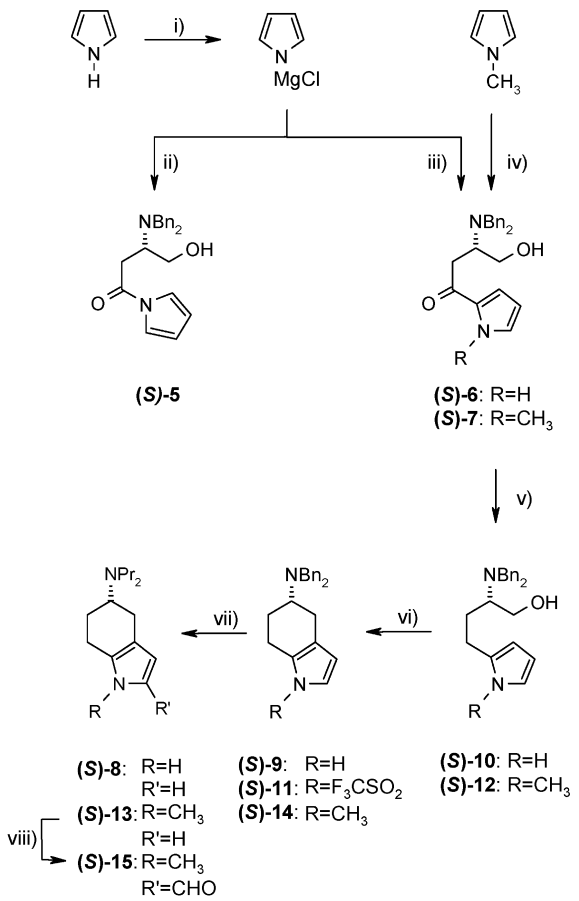
Scheme 1.

Our initial investigations were directed towards the synthesis of the 5-aminotetrahydroindoles of type **4a**. For the preparation of the dibenzylamino substituted lactone (*S*)-**2**, natural asparagine was converted into the *N*,*N*-dibenzyl protected aparagine benzyl ester. Subsequent chemoselective reduction of the ester group and lactonization afforded the chiral building block (*S*)-**2** in 36% overall yield, according to our previously described protocol.[6] To attach (*S*)-**2** to the pyrrole moiety, we tried to exploit a nucleophilic ring-opening reaction with pyrrole lithiated in 2-position (Scheme 2).

To prevent problems with the acidic NH-function, we

Keywords: Ex-chiral pool synthesis; Asparagine; Receptor binding; Aminobutyrolactone.
* Corresponding author. Tel.: +49-9131-8529383; fax: +49-9131-8522585; e-mail address: gmeiner@pharmazie.uni-erlangen.de

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.11.041



Scheme 2. (i) MeMgCl, toluene, 0 °C; (ii) (*S*)-**2** (1.0 equiv.), 0 °C, 30 min (59%); (iii) (*S*)-**2** (0.5 equiv.), 100 °C, 75 min (87%); (iv) (1) *n*-BuLi, TMEDA, THF, room temperature, 15 min, (2) (*S*)-**2**, THF, −78 °C (62%); (v) $AlCl_3$, *t*-$BuNH_2{\times}BH_3$, CH_2Cl_2, 0 °C, 1 h ((*S*)-**10**: 44%; (*S*)-**12**: 73%); (vi) $(F_3CSO_2)_2O$, 4-methyl-2,6-di-*tert*-butylpyridine, CH_2Cl_2, 0 °C to room temperature, 1 h ((*S*)-**9**: 48% and (*S*)-**11**: 18%; (*S*)-**14**: 67%); (vii) (1) $Pd(OH)_2$/C, 1 atm H_2, MeOH–EtOAc (1:1), room temperature, 4 h; (2) $NaBH(OAc)_3$, propionaldehyde, 1,2-DCE, room temperature, 1.75 h ((*S*)-**8**: 78%; (*S*)-**13**: 58%); (viii) $POCl_3$, DMF, 0 °C, 1 h (85%).

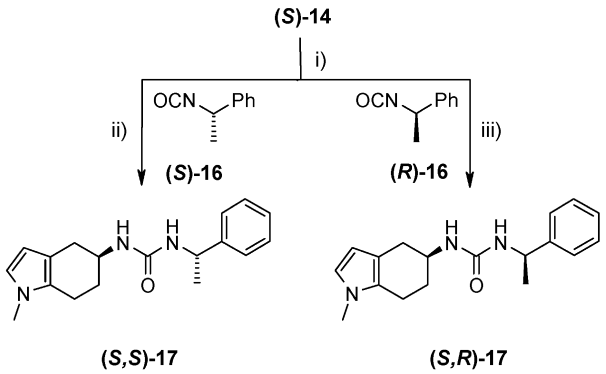
started with *N*-methylpyrrole which was lithiated with *n*-BuLi/TMEDA and subsequently reacted with the lactone (*S*)-**2**.[7] In fact, the reaction proceeded smoothly furnishing the ketone (*S*)-**7** in 62% yield. Employing a mixture of borane–*tert*-butylamine complex and $AlCl_3$ as an effective reducing system,[8] the carbonyl function could be degraded to the methylene unit resulting in formation of the cyclization precursor (*S*)-**12** (73%). Activation of the primary alcohol function with trifluoromethanesulfonic anhydride resulted in a cationic ring closure[9] to afford the *N*-methyltetrahydroindole (*S*)-**14** in 67% yield. It was important to conduct the reaction in presence of 4-methyl-2,6-di-*tert*-butylpyridine as a sterically demanding and effective proton scavenger. By contrast, the use of triethylamine, being previously described for similar aziridinium promoted reactions, gave only 23% yield in this case. 4-Methyl-2,6-di-*tert*-butylpyridine could be easily separated by flash chromatography and recycled for further experiments. The exchange of the benzyl protecting groups with the pharmacophoric propyl substituents was done by catalytic debenzylation followed by a reductive alkylation of the resulting primary amine with propionaldehyde and sodium triacetoxyborohydride to give the test compound (*S*)-**13** in 58% yield.

Starting from dipropylaminotetrahydroindolizines,[4] we recently found that the introduction of a carbaldehyde function into the 2-position of the pyrrole partial structure increased the dopaminergic activity, especially the affinity to the D3 subtype. Therefore, it was interesting for us to see if we could also improve the receptor binding properties by a C-formylation of the tetrahydroindole (*S*)-**13**. We subjected (*S*)-**13** to Vilsmeier conditions and obtained the 2-formyl derivative (*S*)-**15** in 85% yield.

To perform systematic structure–activity-relationship studies, it was also interesting for us to work out a synthesis for the 5-aminotetrahydroindole (*S*)-**8** with a pyrrole NH moiety being putatively involved in hydrogen bonding interaction with the receptor. We first tried the use of N-protected pyrroles including *N*-Ts, *N*-Boc, *N*-SEM and NMe_2 derivatives when activation for a nucleophilic attack should be facilitated by *o*-directed metallation.[10–12] However, lithiation and subsequent treatment with the amino lactone (*S*)-**2** resulted in hardly separable educt/product mixtures and the formation of side products. Thus we turned our attention to a method of Nicolaou et al.[13] when a reagent derived from MeMgCl and pyrrole[14] was used to react with γ-butyrolactone. Depending on the reaction temperature and the stoichiometry, regioselective C–N or C–C bond formation was detected. We observed that pyrrolemagnesium chloride reacted as a *N*-nucleophile with 1.0 equiv. of the lactone (*S*)-**2** at 0 °C to afford the hydroxyamide (*S*)-**5** (59%). On the other hand, employing an excess of the organometallic reagent (2 equiv.) at 100 °C resulted in formation of the ketopyrrole (*S*)-**6** in 87% yield. Obviously, (*S*)-**6** is produced by subsequent N-acylation, *o*-directed metallation and *N*,*C*-acyl migration. Reduction of the carbonyl group afforded the cyclization precursor (*S*)-**10**. Activation of the alcohol function with trifluoromethanesulfonic anhydride led to exclusive *C*-alkylation resulting in formation of the tetrahydroindole (*S*)-**9** as well as the *N*-Tf substituted compound (*S*)-**11** as a side product. The dipropyl derivative (*S*)-**8** was obtained from (*S*)-**9** by hydrogenolytic debenzylation and reductive alkylation in 78% yield. Employing the identical procedures, we synthesized the optical antipodes (*R*)-**8**, (*R*)-**13** and (*R*)-**15** starting from unnatural (*R*)-asparagine.

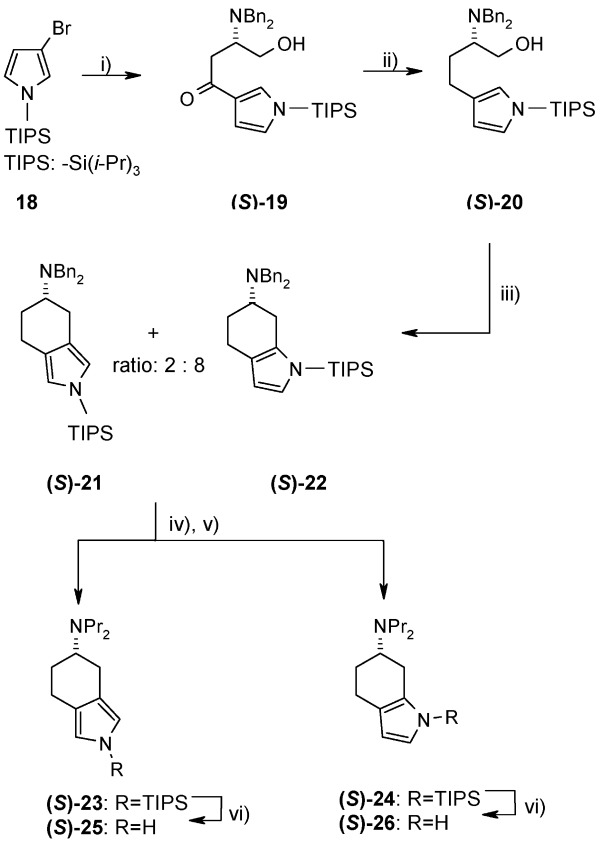
To prove the optical integrity of the reaction pathway by diastereomer formation, coupling with the chiral isocyanates (*S*)-**16** and (*R*)-**16** was done and subsequent HPLC analysis should be performed. Choosing (*S*)-**14** as a representative final product, hydrogenolysis and coupling of the resulting primary amine with the enantiomers (*S*)-**16** and (*R*)-**16** gave the diastereomeric ureas (*S*;*S*)-**17** and (*S*;*R*)-**17**, respectively. Subsequent HPLC analysis including doping experiments indicated a diastereomeric excess >95% (Scheme 3).

For the synthesis of the 6-amino substituted regioisomers of type **4b**, we had to alter the attachment point for the acylation of the pyrrole moiety with the chiral C4 equivalent (*S*)-**2** when metallation in position 3 should be facilitated by halogen metal exchange of the readily available *N*-TIPS



Scheme 3. (i) $Pd(OH)_2/C$, 1 atm H_2, EtOAc–MeOH (1:1), room temperature, 24 h; (ii) (*S*)-**16**, CH_2Cl_2, room temperature, 6 h (66%); (iii) (*R*)-**16**, CH_2Cl_2, room temperature, 6 h (73%).

substituted 3-bromopyrrole **18**.[15] In detail, treatment of **18** with *n*-BuLi at room temperature followed by addition of the amino lactone (*S*)-**2** resulted in formation of the amino alcohol (*S*)-**19** in 47% yield. After reduction of the carbonyl group with borane–*tert*-butylamine in presence of $AlCl_3$, cationic cyclization was induced by activation of the alcohol function with trifluoromethanesulfonic anhydride. Actually, electrophilic attack into the positions 2 and 4 of the aromatic system was observed leading to formation of the tetrahydroindole (*S*)-**22** and the tetrahydroisoindole (*S*)-**21**, respectively, as a 4:1 mixture of nearly separable regioisomers. Exchange of the benzyl groups with propyl substituents via hydrogenolysis and reductive alkylation gave pure (*S*)-**23** (9%) and (*S*)-**24** (62%) after flash chromatography. Finally, fluoride promoted desilylation furnished the final products (*S*)-**25**[16] and (*S*)-**26** in 82 and 69% yield, respectively. Employing the identical procedures, the preparation of the optical antipodes (*R*)-**25** and (*R*)-**26** was performed starting from unnatural (*R*)-asparagine (Scheme 4).



Scheme 4. (i) (1) *n*-BuLi, pentane, room temperature, 15 min; (2) (*S*)-**2**, THF, 0 °C (47%); (ii) $AlCl_3$, *t*-$BuNH_2{\times}BH_3$, CH_2Cl_2, 0 °C, 30 min, (51%); (iii) $(F_3CSO_2)_2O$, 4-methyl-2,6-di-*tert*-butylpyridine, CH_2Cl_2, 0 °C to room temperature, 60 min (79%; (*S*)-**21**–(*S*)-**22**=2:8); (iv) $Pd(OH)_2/C$, 1 atm H_2, MeOH–EtOAc (1:1), room temperature, 2 h; (v) $Na(OAc)_3BH$, propionaldehyde, 1,2-DCE, room temperature, 45 min ((*S*)-**23**: 9%; (*S*)-**24**: 62%); (vi) Bu_4NF, THF, room temperature, 30 min ((*S*)-**25**: 82%; (*S*)-**26**: 69%).

The final products (*S*)-**8**, (*S*)-**13**, (*S*)-**15**, (*S*)-**25**, (*S*)-**26** and their enantiomers we evaluated in vitro for their abilities to displace [^{3}H]spiperone from the cloned human dopamine receptors $D2_{long}$, $D2_{short}$,[17] D3[18] and D4.4[19] being stably expressed in CHO cells (Table 1). D1 affinities were determined by employing porcine striatal membrane preparations and the D1 selective antagonist [^{3}H]SCH23390.[20] As a reference drug, the neurotransmitter dopamine was utilized. All the test compounds investigated

Table 1. Receptor binding data of the tetrahydroindoles **8**, **13**, **15**, **26** and the tetrahydroisoindoles **25** in comparison to the reference compound dopamine at the human dopamine receptor subtypes $D2_{long}$, $D2_{short}$, D3, D4.4 and the porcine D1 receptor (K_i values in nM)

Compound	K_i values (nM)[a]				
	[^{3}H]SCH23390, porcine D1	[^{3}H]spiperone			
		Human $D2_{long}$	Human $D2_{short}$	Human D3	Human D4.4
(*S*)-**8**	35,000[b]	12,000	9700	38+1900[c]	1700
(*R*)-**8**	28,000	28,000	17,000	2000	3000
(*S*)-**13**	16,000	13,000	62+9900	34+1800	610
(*R*)-**13**	16,000	20,000	190+15,000	16,000	3100
(*S*)-**15**	45,000	72,000	56,000	12,000	17,000
(*R*)-**15**	80,000	45,000	65,000	1000	29,000
(*S*)-**25**	24,000	94+11,000	92+6900	33+1100	28+2500
(*R*)-**25**	43,000	28,000	28,000	3700	5400
(*S*)-**26**	21,000	27,000	27,000	7600	20,000
(*R*)-**26**	42,000	36,000	21,000	9400	14,000
Dopamine	7.0+6500	20+1900	17+1100	50+1600	1.2+62

[a] K_i values are the means of 2 to 6 experiments each done in triplicate.
[b] $K_{0.5}$ values derived from the competition curves calculated in a one-site binding mode.
[c] $K_{i\ high}$ and $K_{i\ low}$ values for the high and low affinity binding sites, when the analysis of the dose response curve clearly indicated a biphasic competition.

displayed only weak D1 binding. For all the subtypes investigated, the (*R*)-enantiomers gave K_i values in the micromolar range indicating only moderate affinity. On the other hand, the 5-aminotetrahydroindole (*S*)-**8** showed a biphasic curve for the D3 receptor with a $K_{i\ high}$ of 38 nM indicating high D3 affinity and selectivity as well as agonist properties. While alkylation of the indole-*N* of (*S*)-**8** by a methyl group leading to (*S*)-**13** resulted in a combination of D3 and $D2_{short}$ activity ($K_{i\ high}$=62 nM for $D2_{short}$, $K_{i\ high}$=34 nM for D3), additional formyl substitution in position 2 decreased receptor binding and showed only micromolar affinities as indicated for (*S*)-**15**. This result is in contrast to our recent observations for aminoindolizines when the introduction of a carbaldehyde function gave a beneficial effect.[4] Shifting the propylamino substituent from position 5 to 6 of the tetrahydroindole scaffold as realized in (*S*)-**26**, the receptor recognition was strongly reduced. Interestingly, the tetrahydroisoindole regioisomer (*S*)-**25** revealed substantial receptor affinities to all subtypes of the D2 family with $K_{i\ high}$ values of 94, 92, 33 and 28 nM for $D2_{long}$, $D2_{short}$, D3 and D4, respectively. Considering the absolute configuration of the active enantiomer, this result corroborates previous observations that the pyrroleethylamine moiety, which is part of the BCD tricyclic partial structure of the ergolines, is the active portion of this class of dopamine agonists.[16] To confirm the binding property of the most promising, D3 selective compound (*S*)-**8**, we determined its agonist activity in a mitogenesis assay utilizing D3 expressing CHO dhfr$^-$ cells measuring the increase of [^{3}H]thymidine uptake stimulated by the test compound. The data (EC_{50}=28 nM, agonist effect=55% compared to the effect of the full agonist quinpirol (100%)) clearly indicate agonist properties and, thus, are in agreement with the binding experiments.

In conclusion, chemo- and regioselective transformations of asparagine gave access to optically active 5- and 6-amino tetrahydroindolizines. Additionally, tetrahydroisoindoles were obtained as side products. Receptor binding experiments showed stereocontrolled receptor recognition leading to the D3 selective agonist (*S*)-**8** with D3 binding that is comparable to dopamine. Compounds of this type might be of interest for the treatment of Parkinson's disease.

2. Experimental

2.1. General

Solvents and reagents were purified and dried by standard procedures. Unless otherwise noted reactions were conducted under dry N_2. Evaporations of final product solutions were done under vacuo with a rotatory evaporator. Flash chromatography was carried out with 230–400 mesh silica gel. If not otherwise stated MS were run by EI ionization (70 eV) with solid inlet, HRMS were obtained employing peak matching $M/\Delta M$=10,000. ^{1}H NMR spectra were recorded at 360 MHz spectrometers, if not otherwise stated in $CDCl_3$ relative to TMS; ^{13}C NMR spectra were recorded at 90 MHz in $CDCl_3$. Elemental analyses were performed by Beetz Microanalysis Laboratory and by the Institute of Organic Chemistry (Analytical Departments) of the Friedrich-Alexander University Erlangen-Nürnberg.

2.1.1. (*S*)-3-Dibenzylamino-4-hydroxypyrrol-1-ylbutane-1-one ((*S*)-5). To a solution of methylmagnesium chloride (0.33 mL, 1.0 mmol, 3.0 M in THF) in toluene (5 mL) pyrrole (69 μL, 1.0 mmol) was added dropwise at 0 °C and stirred for 15 min. Then a solution of lactone (*S*)-**2** (281 mg, 1.0 mmol) in toluene (3 mL) was added dropwise and stirred for further 30 min at 0 °C. Then water and CH_2Cl_2 were added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (petroleum ether–EtOAc, 7:3) to give (*S*)-**5** (205 mg, 59%) as a colorless oil: $[\alpha]_D^{20}$=+56.6° (*c*=3.0 $CHCl_3$); IR 3445, 1713 cm^{-1}; ^{1}H NMR (360 MHz) δ 2.65 (s, 1H), 2.79 (dd, *J*=15.0, 8.0 Hz, 1H), 3.14 (dd, *J*=15.0, 5.0 Hz, 1H,), 3.5–3.7 (m, 3H), 3.55 (d, *J*=13.0 Hz, 2H), 3.85 (d, *J*=13.0 Hz, 2H), 6.30 (d, *J*=2.4 Hz, 2H), 7.2–7.3 (m, 2H), 7.2–7.4 (m, 10H); ^{13}C NMR (90 MHz) δ 31.9, 53.5, 56.4, 61.5, 113.3, 118.9, 127.2, 128.1, 128.3, 138.4, 170.9; APCI-MS: 349 (M^+). Anal. Calcd for $C_{22}H_{24}N_2O_2$ (348.45): C, 75.83; H, 6.94; N, 8.04. Found: C, 75.89; H, 6.90; N, 8.07.

2.1.2. (*S*)-3-Dibenzylamino-4-hydroxy-1-(1*H*-pyrrol-2-yl)-butane-1-one ((*S*)-6). To a solution of methylmagnesium chloride (3.33 mL, 10.0 mmol, 3.0 M in THF) in toluene (10 mL) pyrrole (0.83 mL, 12.0 mmol) was added dropwise at 0 °C. The mixture was stirred at 50 °C for 1 h. Then a solution of lactone (*S*)-**2** (1.41 g, 5 mmol) in toluene (10 mL) was added. After stirring for a further 75 min at 100 °C the mixture was allowed to cool to room temperature. Then saturated NH_4Cl and Et_2O were added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (petroleum ether–EtOAc, 7:3) to give (*S*)-**6** (1.51 g, 87%) as a colorless oil: $[\alpha]_D^{20}$=+46.3° (*c*=2.0, $CHCl_3$); IR 3403, 3027, 1634 cm^{-1}; ^{1}H NMR (360 MHz) δ 2.70 (dd, *J*=14.0, 4.0 Hz, 1H), 2.96 (s, 1H), 3.16 (dd, *J*=14.0, 8.0 Hz, 1H), 3.4–3.6 (m, 3H), 3.50 (d, *J*=13.0 Hz, 2H), 3.87 (d, *J*=13.0 Hz, 2H), 6.28 (ddd, *J*=4.0, 2.5, 2.5 Hz, 1H), 6.90 (ddd, *J*=4.0, 2.5, 1.5 Hz, 1H), 7.04 (ddd, *J*=2.5, 2.5, 1.5 Hz, 1H), 7.3–7.5 (m, 10H), 9.56 (s, 1H); ^{13}C NMR (90 MHz) δ 34.8, 53.6, 57.1, 61.8, 110.9, 116.5, 125.00, 127.3, 128.5, 129.0, 131.9, 138.9, 188.8. CIMS 349 (M^+). Anal. Calcd for $C_{22}H_{24}N_2O_2$ (348.45): C, 75.83; H, 6.94; N, 8.04. Found: C, 75.47; H, 7.04; N, 7.69. The enantiomer (*R*)-**6** was prepared as described for (*S*)-**6** using (*R*)-**2**: $[\alpha]_D^{20}$=−47.7° (*c*=1.0, $CHCl_3$).

2.1.3. (*S*)-3-Dibenzylamino-4-hydroxy-1-(1-methyl-pyrrol-2-yl)-butan-1-one ((*S*)-7). TMEDA (4.86 mL, 32.3 mmol) and *N*-methylpyrrole (3.75 mL, 42.1 mmol) were added to *n*-BuLi (20.2 mL, 32.3 mmol, 1.6 M in hexane) and allowed to stir 15 min at room temperature. This mixture was then added dropwise to a solution of (*S*)-**2** (3.04 g, 10.8 mmol) in THF (80 mL) at −78 °C until no more (*S*)-**2** could be detected via TLC (petroleum ether–EtOAc 7:3). Saturated $NaHCO_3$ (20 mL) was added and the reaction mixture was warmed to room temperature. Et_2O and water were added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (petroleum ether–EtOAc, 7:3) to give (*S*)-**7** (2.43 g, 62%) as a colorless oil: $[\alpha]_D^{20}$=+39.6° (*c*=0.5, $CHCl_3$); IR 3447, 1639 cm^{-1}; ^{1}H NMR (360 MHz) δ 2.70 (dd, *J*=14.0, 8.5 Hz, 1H), 2.98 (s, 1H), 3.16 (dd, *J*=14.0,

4.0 Hz, 1H), 3.40–3.60 (m, 1H), 3.40–3.60 (m, 2H), 3.50 (d, J=13.5 Hz, 2H), 3.86 (d, J=13.5 Hz, 2H), 3.93 (s, 3H), 6.13 (dd, J=4.0, 2.5 Hz, 1H), 6.83 (dd, J=2.5, 1.5 Hz, 1H), 6.93 (dd, J=4.0, 1.5 Hz, 1H), 7.20–7.35 (m, 10H); ^{13}C NMR (90 MHz) δ 36.0, 37.7, 53.6, 57.2, 61.8, 108.1, 119.6, 127.3, 128.5, 129.0, 130.6, 131.6, 139.0, 189.4; CIMS 362 (M^+). Anal. Calcd for $C_{23}H_{26}N_2O_2$ (362.48): C, 76.21; H, 7.23; N, 7.73. Found: C, 76.34; H, 7.34; N, 7.74. The enantiomer (*R*)-**7** was prepared as described for (*S*)-**7** using (*R*)-**2**: $[\alpha]_D^{20}=-41.5°$ (c=0.5, $CHCl_3$).

2.1.4. (*S*)-5-Dipropylamino-4,5,6,7-tetrahydroindole ((*S*)-8). Compound (*S*)-**8** was prepared as described for (*S*)-**13** using (*S*)-**9** (45 mg, 0.142 mmol). The residue was purified by flash chromatography (CH_2Cl_2–MeOH 9:1) to give (*S*)-**8** (24 mg, 78%) as a colorless oil: $[\alpha]_D^{20}=-49.5°$ (c=1.0, $CHCl_3$); ^{1}H NMR (360 MHz) δ 0.89 (t, J=7.4 Hz, 6H, $CH_2CH_2CH_3$), 1.5–1.6 (m, 4H, $CH_2CH_2CH_3$), 1.7 (m, 1H, H-6_{ax}), 2.1 (m, 1H, H-6_{eq}), 2.5–2.6 (m, 4H, CH_2CH_2-CH_3), 2.6–2.7 (m, 4H, H-$4_{eq,ax}$, H-$7_{eq,ax}$), 3.0–3.1 (m, 1H, H-5_{ax}), 5.97 (dd, J=2.7, 2.7 Hz, 1H, H-3), 6.63 (dd, J=2.7, 2.7 Hz, 1H, H-2), 7.80 (s, 1H, NH); ^{13}C NMR (90 MHz) δ 11.85 ($NCH_2CH_2CH_3$), 21.68 ($NCH_2CH_2CH_3$), 22.82, 24.53 (C-4, C-7), 26.09 (C-6), 52.83 ($NCH_2CH_2CH_3$), 58.26 (C-5), 107.66 (C-3), 116.00 (C-3a), 116.52 (C-2), 126.13 (C-7a); EIMS 220 (M^+). Anal. Calcd for $C_{14}H_{24}N_2$ (220.36): C, 76.31; H, 10.98; N, 12.71. Found: C, 76.25; H, 10.99; N, 12.66. The enantiomer (*R*)-**8** was prepared as described for (*S*)-**13** using (*R*)-**9**: $[\alpha]_D^{20}=+50.0°$ (c=0.5, $CHCl_3$).

2.1.5. (*S*)-5-Dibenzylamino-4,5,6,7-tetrahydro-1*H*-indole ((*S*)-9) and (*S*)-1-trifluoromethylsulfonyl-5-dibenzylamino-4,5,6,7-tetrahydro-1*H*-indole ((*S*)-11). Trifluoromethanesulfonic anhydride (0.59 mL, 3.60 mmol) was added dropwise to an ice cooled solution of (*S*)-**10** (926 mg, 2.77 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (1.48 g, 7.20 mmol). The mixture was stirred for 1 h at room temperature. Then saturated $NaHCO_3$ and CH_2Cl_2 were added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (petroleum ether–EtOAc, 9:1) to give (*S*)-**9** (423 mg, 48%) and (*S*)-**11** (220 mg, 18%) as colorless oils: (*S*)-**9**: $[\alpha]_D^{20}=-58.9°$ (c=2.0, $CHCl_3$); ^{1}H NMR (360 MHz) δ 1.81 (dddd, J=12.5, 12.0, 12.0, 6.0 Hz, 1H), 2.14 (ddd, J=12.5, 2.5, 2.2 Hz, 1H), 2.5–2.7 (m, 4H), 3.01 (dddd, J=12.0, 10.0, 6.0, 2.2 Hz, 1H), 3.66 (d, J=14.0 Hz, 2H), 3.75 (d, J=14.0 Hz, 2H), 5.96 (dd, J=2.6, 2.6 Hz, 1H), 6.59 (dd, J=2.6, 2.6 Hz, 1H), 7.3–7.5 (m, 10H), 7.64 (s, 1H); ^{13}C NMR (90 MHz) δ 22.9, 24.4, 25.4, 54.0, 54.3, 115.0, 122.4, 125.2, 126.8, 128.3, 128.4, 130.4, 140.4. EIMS 316 (M^+). Anal. Calcd for $C_{22}H_{24}N_2$ (316.45): C, 83.50; H, 7.64; N, 8.85. Found: C, 83.49; H, 7.65; N, 8.87. (*S*)-**11**: $[\alpha]_D^{20}=-11.5°$ (c=2.0, $CHCl_3$); ^{1}H NMR (360 MHz) δ 1.76 (dddd, J=12.5, 12.0, 12.0, 5.3 Hz, 1H), 2.20 (ddd, J=12.5, 5.3, 2.4 Hz, 1H), 2.5–2.7 (m, 4H), 2.9–3.0 (m, 1H), 3.65 (d, J=14.0 Hz, 2H), 3.74 (d, J=14.0 Hz, 2H), 6.16 (d, J=3.5 Hz, 1H), 6.94 (d, J=3.5 Hz, 1H), 7.2–7.5 (m, 10H); ^{13}C NMR (90 MHz) δ 22.9, 24.4, 25.4, 53.9, 54.3, 115.0, 119.3 (q, J=323 Hz), 122.4, 125.2, 126.8, 128.2, 128.4, 130.4, 140.3;. EIMS 448 (M^+). Anal. Calcd for $C_{23}H_{23}F_3N_2O_2S$ (448.51): C, 61.59; H, 5.17; N, 6.25. Found: C, 61.55; H, 5.18; N, 6.20. The enantiomers (*R*)-**9** and (*R*)-**11** were prepared as described for (*S*)-**9** and (*S*)-**11** using (*R*)-**10**: (*R*)-**9**: $[\alpha]_D^{20}=+57.2°$ (c=3.0, $CHCl_3$); (*R*)-**11**: $[\alpha]_D^{20}=+13.4°$ (c=3.0, $CHCl_3$).

2.1.6. (*S*)-2-Dibenzylamino-4-(1*H*-pyrrol-2-yl)-butan-1-ol ((*S*)-10). $AlCl_3$ (2.62 g, 19.70 mmol) was suspended in CH_2Cl_2 (90 mL) and cooled to 0 °C. Borane–*tert*butylamine complex (3.43 g, 39.40 mmol) was slowly added. The mixture was allowed to stir for 10 min giving a clear colorless solution. A solution of (*S*)-**6** (2.29 g; 6.57 mmol) in as little CH_2Cl_2 as can be was added dropwise to the ice-cooled solution and stirred for a further 60 min. Then water was carefully added at 0 °C. The solution was warmed up to room temperature and 0.1 M HCl was added until the gas evolution stopped. Then CH_2Cl_2 was added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (petroleum ether–EtOAc, 7:3) to give (*S*)-**10** (959 mg, 44%) as a colorless oil: $[\alpha]_D^{20}=+70.0°$ (c=1.0, $CHCl_3$); IR 3427, 3376 cm^{-1}; ^{1}H NMR (360 MHz) δ 1.54 (dddd, J=13.5, 9.0, 8.0, 6.0 Hz, 1H), 2.04 (dddd, J=13.5, 9.0, 7.0, 4.0 Hz, 1H), 2.52 (ddd, J=15.0, 8.0, 7.0 Hz, 1H), 2.63 (ddd, J=15.0, 9.0, 6.0 Hz, 1H), 2.83 (dddd, J=9.0, 9.0, 5.5, 4.0 Hz, 1H), 2.92 (s, 1H), 3.4–3.6 (m, 2H), 3.43 (d, J=14.0 Hz, 2H), 3.79 (d, J=14.0 Hz, 2H), 5.93 (ddd, J=3.5, 2.5, 1.5 Hz, 1H), 6.14 (ddd, J=3.5, 3.0, 1.5 Hz, 1H), 6.63 (ddd, J=3.0, 2.5, 1.5 Hz, 1H), 7.3–7.5 (m, 10H), 7.80 (s, 1H); ^{13}C NMR (90 MHz) δ 25.1, 25.9, 53.3, 58.4, 60.9, 105.2, 108.5, 116.3, 127.2, 128.5, 129.1, 131.6, 139.3; EIMS 334 (M^+). Anal. Calcd for $C_{22}H_{26}N_2O$ (334.37): C, 79.01; H, 7.84; N, 8.38. Found: C, 78.98; H, 7.82; N, 8.07. The enantiomer (*R*)-**10** was prepared as described for (*S*)-**10** using (*R*)-**6**: $[\alpha]_D^{20}$-69.0° (c=1.0, $CHCl_3$).

2.1.7. (*S*)-2-Dibenzylamino-4-(1-methyl-1*H*-pyrrol-2-yl)-butan-1-ol ((*S*)-12). $AlCl_3$ (1.16 g, 8.70 mmol) was suspended in CH_2Cl_2 (30 mL) and cooled to 0 °C. Borane–*tert*butylamine complex (1.51 g, 17.4 mmol) was added slowly. The mixture was allowed to stir for 10 min giving a clear colorless solution. A solution of (*S*)-**7** (1.05 g; 2.90 mmol) in as little CH_2Cl_2 as can be was added dropwise to the ice-cooled solution and stirred for a further 60 min. Then water was carefully added at 0 °C. The solution was warmed up to room temperature and 0.1 M HCl was added until the gas evolution stopped. Then CH_2Cl_2 was added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography ($CHCl_3$–EtOAc, 95:5) to give (*S*)-**12** (734 mg, 73%) as a colorless oil: $[\alpha]_D^{20}=+92.0°$ (c=1.0, $CHCl_3$); IR 3439 cm^{-1}; ^{1}H NMR (360 MHz) δ 1.55 (dddd, J=13.5, 9.5, 9.0, 5.5 Hz, 1H), 2.07 (dddd, J=13.5, 10.0, 6.5, 4.0 Hz, 1H), 2.45 (ddd, J=15.5, 9.0, 6.5 Hz, 1H) 2.52 (ddd, J=15.5, 10.0, 5.5 Hz, 1H), 2.87 (dddd, J=9.5, 9.5, 5.5, 4.0 Hz, 1H), 3.04 (s, 1H), 3.43 (d, J=13.0 Hz, 2H), 3.50 (s, 3H), 3.5–3.6 (m, 2H), 3.83 (d, J=13.0 Hz, 2H), 5.91 (dd, J=3.0, 2.0 Hz, 1H), 6.07 (dd, J=3.0, 2.5 Hz, 1H), 6.56 (dd, J=2.5, 2.0 Hz, 1H), 7.2–7.4 (m, 10H); ^{13}C NMR (90 MHz) δ 23.9, 24.6, 33.5, 53.2, 58.8, 60.8, 105.6, 106.8, 121.3, 127.2, 128.5, 129.1, 132.5, 139.2; EIMS 348 (M^+). Anal. Calcd for $C_{23}H_{28}N_2O$ (348.49): C, 79.27; H, 8.10; N, 8.04. Found: C, 79.01; H, 7.95; N, 7.89. The enantiomer (*R*)-**12** was prepared as

described for (*S*)-**12** using (*R*)-**7**: $[\alpha]_D^{20}=-91.5°$ (c=1.0, $CHCl_3$).

2.1.8. (*S*)-5-Dipropylamino-1-methyl-4,5,6,7-tetrahydroindole ((*S*)-13). A solution of (*S*)-**14** (386 mg, 1.17 mmol) and $Pd(OH)_2$/C (333 mg) in EtOAc and MeOH (1:1) (20 mL) was stirred under hydrogen atmosphere (1 atm) at room temperature for 24 h. The solution was filtered and evaporated to give the crude amine (176 mg). The crude product was dissolved in 1,2-dichloroethane (20 mL), propionaldehyde (0.17 mL, 2.34 mmol) and sodium triacetoxyborohydride (595 mg, 2.81 mmol) were added. After stirring for 1 h at room temperature, $NaHCO_3$ and CH_2Cl_2 were added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (CH_2Cl_2–MeOH 9:1) to give (*S*)-**13** (160 mg, 58%) as a colorless oil: $[\alpha]_D^{20}=-48.4°$ (c=0.25, $CHCl_3$); ^{1}H NMR (360 MHz) δ 0.87 (t, J=7.5 Hz, 6H, $NCH_2CH_2CH_3$), 1.45 (tq, J=7.5, 7.5 Hz, 4H, $NCH_2CH_2CH_3$), 1.69 (dddd, J=12.0, 12.0, 12.0, 6.0 Hz, 1H, H-6_{ax}), 2.02 (dddd, J=12.0, 6.0, 4.0, 2.0 Hz, 1H, H-6_{eq}), 2.4–2.5 (m, 4H, $NCH_2CH_2CH_3$), 2.4–2.7 (m, 4H, H-4, H-7), 2.95 (dddd, J=12.0, 11.5, 5.0, 2.0 Hz, H-5_{ax}), 3.46 (s, 3H, NCH_3), 5.89 (d, J=2.5 Hz, 1H, pyrrole-H-3), 6.48 (d, J=2.5 Hz, 1H, pyrrole-H-2); ^{13}C NMR (90 MHz) δ 11.84 ($NCH_2CH_2CH_3$), 21.82, 24.71 ($NCH_2CH_2CH_3$, C-4, C-7), 26.02 (C-6), 33.03 (NCH_3), 52.81 ($NCH_2CH_2CH_3$), 57.93 (C-5), 106.11 (C-3), 116.34 (C-3a), 120.39 (C-2), 127.43 (C-7a); EIMS 234 (M^+); combustion analysis from the dibenzoyl-L-tartaric acid salt (mp 107 °C). Anal. Calcd for $C_{33}H_{40}N_2O_2$ (592.69): C, 72.47; H, 11.77; N, 7.35. Found: C, 72.53; H, 11.69; N, 7.29; HRMS calcd for $C_{15}H_{26}N_2$ (M^+): 234.20997. Found: 234.20959. The enantiomer (*R*)-**13** was prepared as described for (*S*)-**13** using (*R*)-**14**: $[\alpha]_D^{20}=+49.4°$ (c=1.0, $CHCl_3$).

2.1.9. (*S*)-5-Dibenzylamino-1-methyl-4,5,6,7-tetrahydroindole ((*S*)-14). Trifluoromethanesulfonic anhydride (0.48 mL, 2.94 mmol) was added dropwise to an ice cooled solution of (*S*)-**12** (682 mg, 1.96 mmol) and 2,6-di-*tert*-butyl-4-methyl-pyridine (1.21 g, 5.88 mmol). The mixture was stirred for 1 h at room temperature. Then saturated $NaHCO_3$ and CH_2Cl_2 were added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (petroleum ether–EtOAc, 9:1) to give (*S*)-**14** (433 mg, 67%) as a colorless oil: $[\alpha]_D^{20}=-47.0°$ (c=1.0, $CHCl_3$); ^{1}H NMR (360 MHz) δ 1.79 (dddd, J=12.0, 12.0, 12.0, 5.5 Hz, 1H), 2.17 (m, 1H), 2.44 (m, 1H), 2.60–2.76 (m, 3H), 2.98 (dddd, J=12.0, 10.0, 6.0, 2.5 Hz, 1H), 3.40 (s, 3H), 3.66 (d, J=14.0 Hz, 2H), 3.73 (d, J=14.0 Hz, 2H), 5.88 (d, J=2.5 Hz, 1H), 6.44 (d, J=2.5 Hz, 1H), 7.10–7.40 (m, 10H, ArH); ^{13}C NMR (90 MHz) δ 21.6, 24.7, 24.9, 32.8, 53.8, 55.1, 105.9, 116.5, 120.1, 126.4, 127.3, 128.0, 128.3, 140.7; EIMS 330 (M^+). Anal. Calcd for $C_{23}H_{26}N_2$ (330.48): C, 83.59; H, 7.93; N, 8.48. Found: C, 83.56; H, 7.76; N, 8.37. The enantiomer (*R*)-**14** was prepared as described for (*S*)-**14** using (*R*)-**12**: $[\alpha]_D^{20}=+47.5°$ (c=1.0, $CHCl_3$).

2.1.10. (*S*)-5-Dipropylamino-1-methyl-4,5,6,7-tetrahydroindol-2-carbaldehyde ((*S*)-15). $POCl_3$ (36 μL, 0.392 mmol) was added at 0 °C to a solution of (*S*)-**13** (46 mg, 0.196 mmol) in DMF (5 mL). The reaction mixture was stirred for a further 60 min. After that the reaction solution was added to ice cooled 1 N NaOH and the product was extracted with Et_2O. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (CH_2Cl_2–MeOH 9:1) to give (*S*)-**15** (44 mg, 85%) as a colorless oil: $[\alpha]_D^{20}=-65.5°$ (c=0.4, $CHCl_3$); IR 1654 cm^{-1}; ^{1}H NMR (360 MHz) δ 0.89 (t, J=7.5 Hz, 6H, $NCH_2CH_2CH_3$), 1.3–1.5 (m, 4H, $NCH_2CH_2CH_3$), 1.6–1.7 (m, 1H, H-6_{ax}), 2.0–2.1 (m, 1H, H-6_{eq}), 2.4–2.5 (m, 4H, $NCH_2CH_2CH_3$), 2.4–2.8 (m, 4H, H-4, H-7), 2.8–3.0 (m, 1H, H-5_{ax}), 3.80 (s, 3H, NCH_3), 6.64 (m, 1H, pyrrole-H-3), 9.38 (s, 1H, CHO); ^{13}C NMR (90 MHz) δ 11.84 ($NCH_2CH_2CH_3$), 22.01, 22.19, 24.88 ($NCH_2CH_2CH_3$, C-4,C-7), 25.41 (C-6), 32.18 (NCH_3), 52.78 ($NCH_2CH_2CH_3$), 57.33 (C-5), 119.76 (C-3a), 122.84 (C-3), 131.42 (C-7a), 139.60 (C-2), 178.54 (CHO); EIMS 262 (M^+). Anal. Calcd for $C_{16}H_{26}N_2O$ (262.40): C, 73.24; H, 9.99; N, 10.68. Found: C, 72.91; H, 10.00; N, 10.65. The enantiomer (*R*)-**15** was prepared as described for (*S*)-**15** using (*R*)-**13**: $[\alpha]_D^{20}=+63.5°$ (c=0.5, $CHCl_3$).

2.1.11. 1-[(*S*)-1-Methyl-4,5,6,7-tetrahydro-1*H*-indol-5-yl]-3-[(*S*)-phenylethyl]-urea ((*S*,*S*)-17) and 1-[(*S*)-1-methyl-4,5,6,7-tetrahydro-1*H*-indol-5-yl]-3-[(*R*)-phenylethyl]-urea ((*S*,*R*)-17). Compound (*S*)-**14** (83 mg, 0.251 mmol) and $Pd(OH)_2$/C (83 mg), dissolved in EtOAc–MeOH (9:1, 5 mL), were stirred for 24 h at room temperature under hydrogen atmosphere (1 atm). After removing the catalyst by filtration, the solution was divided in two equal parts and evaporated separately. (*R*)-Phenylethyl isocyanate (*R*)-**16** (17 μL, 0.123 mmol) was added to a solution of one part of the residue (14 mg, 0.092 mmol) in CH_2Cl_2 (3 mL). After stirring for 6 h at room temperature, the solvent was removed and the residue was purified by flash chromatography (CH_2Cl_2–MeOH 9:1) to give (*S*;*R*)-**17** (20 mg, 73%) as a colorless oil. (*S*)-Phenylethyl isocyanate (17 μL, 0.123 mmol) was added to a solution of the second part of the residue (17 mg, 0.112 mmol) in CH_2Cl_2 (3 mL). After stirring for 6 h at room temperature, the solvent was removed and the residue was purified by flash chromatography (CH_2Cl_2–MeOH 9:1) to give (*S*,*S*)-**17** (22 mg, 66%) as a colorless oil. An analytical sample was prepared: (*S*,*S*)-**17**: $[\alpha]_D^{20}=-13.1°$ (c=0.7, $CHCl_3$); IR 3332, 1623 cm^{-1}; ^{1}H NMR (360 MHz) δ 1.45 (d, J=6.8 Hz, 3H), 1.82 (m, 1H), 1.97 (m, 1H), 2.25 (m, 1H), 2.45–2.80 (m, 3H), 3.45 (s, 3H), 4.05 (m, 1H), 4.25 (d, J=7.5 Hz, 1H), 4.42 (d, J=7.5 Hz, 1H), 4.79 (m, 1H), 5.84 (d, J=2.7 Hz, 1H), 6.47 (d, J=2.7 Hz, 1H), 7.2–7.4 (m, 5H); EIMS 297 (M^+). Anal. Calcd for $C_{18}H_{23}N_3O$ (297.40): C, 72.70; H, 7.80; N, 14.13. Found: C, 72.44; H, 7.68; N, 14.25. (*S*,*R*)-**17**: IR 3330, 1627 cm^{-1}; ^{1}H NMR (360 MHz) δ 1.42 (d, J=6.8 Hz, 3H), 1.81 (dddd, J=15.0, 13.1, 13.0, 6.7 Hz, 1H), 2.17 (m, 1H), 2.34 (dd, J=15.5, 6.0 Hz, 1H), 2.44 (dd, J=15.5, 12.4 Hz, 1H), 2.3–2.5, 2.7–2.9 (m, 2H), 3.39 (s, 3H), 4.05 (m, 1H), 4.33 (d, J=8.6 Hz, 1H), 4.53 (d, J=5.8 Hz, 1H), 4.67 (ddd, J=13.0, 12.4, 6.0 Hz, 1H), 5.85 (d, J=2.7 Hz, 1H), 6.46 (d, J=2.7 Hz, 1H), 7.2–7.4 (m, 5H, ArH);. EIMS 297 (M^+); HRMS calcd for $C_{18}H_{23}N_3O$ (M^+): 297.18411. Found: 297.18418. HPLC (Lichrosorb Si 60 7μ, CH_2Cl_2–MeOH 99:1, 1.5 mL min^{-1}, detection UV: 256 nm) t_R 13.0 min (97.5%, (*S*,*R*)-**17**), 10.2 min (2.5%, (*S*,*S*)-**17**).

2.1.12. (*S*)-3-Dibenzylamino-4-hydroxy-(1-triisopropylsilyl-1*H*-pyrrol-3-yl)-butan-1-one ((*S*)-19). To a solution of 3-bromo-1-triisopropylsilyl pyrrole (605 mg, 2.0 mmol) in pentane (5 mL), *n*-BuLi (1.25 mL, 2.0 mmol, 1.6 M in hexane) was added dropwise. The mixture was stirred for 15 min at room temperature. The solution was then slowly added to (*S*)-**2** (281 mg, 1.0 mmol) dissolved in THF (5 mL) at 0 °C. The addition was stopped, when no more lactone (*S*)-**2** could be detected via TLC (petroleum ether–Et_2O 1:1). Then water and Et_2O were added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (petroleum ether -Et_2O 1:1) to give (*S*)-**19** (234 mg, 47%) as a colorless oil: $[\alpha]_D^{20}$+50.0° (*c*=0.5, $CHCl_3$); IR 3445, 1652 cm^{-1}; ^1H NMR (360 MHz) δ 1.11 (d, *J*=7.5 Hz, 18H), 1.47 (qq, *J*=7.5, 7.5 Hz, 3H), 2.70 (dd, *J*=14.5, 7.7 Hz, 1H), 3.05 (s, 1H), 3.14 (dd, *J*=14.5, 4.3 Hz, 1H), 3.53 (d, *J*=13.4 Hz, 2H), 3.5–3.6 (m, 3H), 3.85 (d, *J*=13.4 Hz, 2H), 6.70 (dd, *J*=3.0, 1.5 Hz, 1H), 6.75 (dd, *J*=3.0, 2.0 Hz, 1H), 7.2–7.4 (m, 10H), 7.39 (dd, *J*=2.0, 1.5 Hz, 1H); ^{13}C NMR (90 MHz) δ 11.3, 17.4, 36.6, 53.4, 56.6, 61.7, 110.7, 125.5, 127.0, 127.8, 128.2, 128.8, 129.3, 139.0, 194.6. Anal. Calcd for $C_{31}H_{44}N_2O_2Si$ (504.79): C, 73.76; H, 8.79; N, 5.55. Found: C, 73.83; H, 8.70; N, 5.59. The enantiomer (*R*)-**19** was prepared as described for (*S*)-**19** using (*R*)-**2**: $[\alpha]_D^{20}$=−48.5° (*c*=0.5, $CHCl_3$).

2.1.13. (*S*)-2-Dibenzylamino-4-(1-triisopropylsilyl-1*H*-pyrrol-3-yl)-butan-1-ol ((*S*)-20). Compound (*S*)-**20** was prepared as described for (*S*)-**12** using (*S*)-**19** (1.44 g, 2.86 mmol). The residue was purified by flash chromatography (petroleum ether–Et_2O, 8:2) to give (*S*)-**20** (721 mg, 51%) as a colorless oil: $[\alpha]_D^{20}$=+80.9° (*c*=2.0, $CHCl_3$); IR 3449 cm^{-1}; ^1H NMR (360 MHz) δ 1.09 (d, *J*=7.5 Hz, 18H), 1.44 (qq, *J*=7.5, 7.5 Hz, 3H), 1.4–1.5 (m, 1H), 2.04 (dddd, *J*=13.5, 9.5, 6.5, 4.0 Hz, 1H), 2.45 (ddd, *J*=14.5, 9.0, 6.5 Hz, 1H), 2.52 (ddd, *J*=14.5, 9.5, 5.5 Hz, 1H), 2.86 (dddd, *J*=9.5, 9.5, 4.5, 4.0 Hz, 1H), 3.14 (s, 1H), 3.4–3.6 (m, 2H), 3.44 (d, *J*=13.5 Hz, 2H), 3.81 (d, *J*=13.5 Hz, 2H), 6.17 (dd, *J*=2.5, 1.5 Hz, 1H), 6.52 (dd, *J*=2.0, 1.5 Hz, 1H), 6.72 (dd, *J*=2.5, 2.0 Hz, 1H), 7.2–7.4 (m, 10H); ^{13}C NMR (90 MHz) δ 11.6, 17.7, 24.7, 26.7, 53.2, 59.0, 60.9, 110.4, 121.0, 124.3, 125.3, 127.1, 128.4, 129.1, 139.5; EIMS 490 (M^+). Anal. Calcd for $C_{31}H_{46}N_2OSi$ (490.81): C, 75.86; H, 9.45; N, 5.71. Found: C, 75.60; H, 9.51; N, 5.71. The enantiomer (*R*)-**20** was prepared as described for (*S*)-**12** using (*R*)-**19**: $[\alpha]_D^{20}$=−79.6° (*c*=2.0, $CHCl_3$).

2.1.14. (*S*)-6-Dibenzylamino-1-triisopropylsilyl-4,5,6,7-tetrahydro-1*H*-indole ((*S*)-22), (*S*)-5-dibenzylamino-2-triisopropylsilyl-4,5,6,7-tetrahydro-2*H*-isoindole ((*S*)-21). Compounds (*S*)-**22** and (*S*)-**21** were prepared as described for (*S*)-**14** using (*S*)-**20** (730 mg, 1.49 mmol). The residue was purified by flash chromatography (petroleum ether–Et_2O, 100:0, 98:2, 95:5) to give a 8:2 mixture (estimated by ^1H NMR) of (*S*)-**22** and (*S*)-**21** (556 mg, 79%) as a colorless oil: (*S*)-**22**: ^1H NMR (360 MHz) δ 1.09 (d, *J*=7.5 Hz, 18H), 1.46 (qq, *J*=7.5, 7.5 Hz, 3H), 1.73 (dddd, *J*=12.0, 12.0, 12.0, 5.5 Hz, 1H), 2.0–2.1 (m, 1H), 2.4–2.5 (m, 1H), 2.4–2.5 (m, 1H), 2.6–2.7 (m, 1H), 2.8–2.9 (m, 1H), 3.02 (dddd, *J*=12.0, 11.0, 4.5, 2.0 Hz, 1H), 3.66 (d, *J*=14.0 Hz, 2H), 3.76 (d, *J*=14.0 Hz, 2H), 5.97 (d, *J*=2.5 Hz, 1H), 6.64 (d, *J*=2.5 Hz, 1H), 7.2–7.5 (m, 10H); (*S*)-**21**: ^1H NMR (360 MHz) δ 6.36 (s, 1H), 6.40 (s, 1H). EIMS 472 (M^+); The enantiomers (*R*)-**22** and (*R*)-**21** were prepared as described for (*S*)-**14** using (*R*)-**20**.

2.1.15. (*S*)-6-Dipropylamino-1-triisopropylsilyl-4,5,6,7-tetrahydro-1*H*-indole ((*S*)-24), (*S*)-5-dipropylamino-2-triisopropylsilyl-4,5,6,7-tetrahydro-2*H*-isoindole ((*S*)-23). A solution of (*S*)-**21** and (*S*)-**22** (563 mg, 1.19 mmol) and $Pd(OH)_2/C$ (563 mg) in EtOAc and MeOH (1:1) was stirred under hydrogen atmosphere (1 atm) at room temperature for 2 h. The solution was filtered and evaporated to give the crude amines (307 mg). The crude product was dissolved in 1,2-dichloroethane, propionaldehyde (0.17 mL, 2.38 mmol) and sodium triacetoxyborohydride (605 mg, 2.86 mmol) were added. After stirring for 45 min at room temperature, $NaHCO_3$ and CH_2Cl_2 were added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (CH_2Cl_2–MeOH 9:1) to give (*S*)-**24** (278 mg, 62%) and (*S*)-**23** (40 mg, 9%) as colorless oils: (*S*)-**24**: $[\alpha]_D^{20}$=−29.8° (*c*=0.5, $CHCl_3$); ^1H NMR (360 MHz) δ 0.89 (t, *J*=7.2 Hz, 6H), 1.11 (d, *J*=7.5 Hz, 18H),1.3–1.7 (m, 8H), 1.9–2.1 (m, 1H), 2.4–2.8 (m, 8H), 3.0 (m, 1H), 6.02 (d, *J*=2.7 Hz, 1H), 6.69 (d, *J*=2.7 Hz, 1H); ^{13}C NMR (90 MHz) δ 11.8, 12.5, 18.2, 22.0, 23.0, 26.2, 27.7, 52.9, 58.2, 108.8, 119.9, 124.6, 131.5; EIMS 376 (M^+). Anal. Calcd for $C_{23}H_{44}N_2Si$ (376.71)×1/4H_2O: C, 72.47; H, 11.77; N, 7.35. Found: C, 72.53; H, 11.69; N, 7.29. (*S*)-**23**: $[\alpha]_D^{20}$=−35.8° (*c*=0.5, $CHCl_3$); ^1H NMR (360 MHz) δ 0.88 (t, *J*=7.2 Hz, 6H), 1.08 (d, *J*=7.5 Hz, 18H),1.39 (q, *J*=7.5 Hz, 3H), 1.4–1.5 (m, 4H), 1.5–1.7 (m, 1H), 1.9–2.0 (m, 1H), 2.5–2.6 (m, 4H), 2.5–2.9 (m, 4H), 3.0–3.1 (m, 1H), 6.40 (s, 1H), 6.42 (s, 1H); EIMS 376 (M^+). Anal. Calcd for $C_{23}H_{44}N_2Si$ (376.71)×1/2H_2O: C, 71.62; H, 11.76; N, 7.26. Found: C, 71.43; H, 11.76; N, 7.29. The enantiomers (*R*)-**23** and (*R*)-**24** were prepared as described for (*S*)-**24** and (*S*)-**23** using (*R*)-**21**/(*R*)-**22**: (*R*)-**24**: $[\alpha]_D^{20}$=+31.3° (*c*=1.5, $CHCl_3$); (*R*)-**23**: $[\alpha]_D^{20}$=+35.5° (*c*=0.5, $CHCl_3$).

2.1.16. (*S*)-5-Dipropylamino-4,5,6,7-tetrahydro-2*H*-isoindole ((*S*)-25). Compound (*S*)-**25** was prepared as described for (*S*)-**26** using (*S*)-**23** (27 mg, 0.072 mmol). The residue was purified by flash chromatography (CH_2Cl_2–MeOH 8:2) to give (*S*)-**25** (13 mg, 82%) as a colorless oil: $[\alpha]_D^{20}$=−52.1° (*c*=0.5, $CHCl_3$); ^1H NMR (360 MHz) δ 0.88 (t, *J*=7.5 Hz, 6H, $NCH_2CH_2CH_3$), 1.50 (tq, *J*=7.5, 7.5 Hz, 4H, $NCH_2CH_2CH_3$), 1.61 (dddd, *J*=12.0, 12.0, 12.0, 5.0 Hz, 1H, H-6_{ax}), 2.0 (m, 1H, H-6_{eq}), 2.4–2.5 (m, 4H, $NCH_2CH_2CH_3$), 2.5–2.7 (m, 2H, H-$7_{eq,ax}$), 2.7–2.9 (m, 2H, H-$4_{eq,ax}$), 2.99 (dddd, *J*=12.0, 12.0, 5.0, 2.0 Hz, 1H, H-5_{ax}), 6.47, 6.49 (s, 2H, H-1, H-3), 8.03 (s, 1H, NH).; ^{13}C NMR (90 MHz) δ 11.91 ($NCH_2CH_2CH_3$), 22.03, 22.19 ($NCH_2CH_2CH_3$, C-7), 24.38 (C-4), 27.01 (C-6), 52.83 ($NCH_2CH_2CH_3$), 58.59 (C-5), 112.85, 113.53 (C-3a, C-7a), 119.09, 119.46 (C-1, C-3); EIMS 220 (M^+); HRMS calcd for $C_{14}H_{24}N_2$ (M^+): 220.19395. Found: 220.19379. The enantiomer (*R*)-**25** was prepared as described for (*S*)-**26** using (*R*)-**23**: $[\alpha]_D^{20}$=+53.6° (*c*=0.8, $CHCl_3$).

2.1.17. (*S*)-6-Dipropylamino-4,5,6,7-tetrahydro-1*H*-indole ((*S*)-26). A solution of (*S*)-**24** (45 mg, 0.119 mmol) and TBAF (119 μL, 0.119 mmol, 1.0 M in THF) in THF

(5 mL) was stirred at room temperature for 20 min. Then, satd $NaHCO_3$ solution and Et_2O were added. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (CH_2Cl_2–MeOH 8:2) to give (*S*)-**26** (18 mg, 69%) as a colorless oil: $[\alpha]_D^{20}=-52.0°$ (c=1.0, $CHCl_3$); ^{1}H NMR (360 MHz) δ 0.88 (t, J=7.5 Hz, 6H, $NCH_2CH_2CH_3$), 1.49 (tq, J=7.5, 7.5 Hz, 4H, $NCH_2CH_2CH_3$), 1.63 (dddd, J=12.0, 12.0, 12.0, 5.5 Hz, 1H, H-5$_{ax}$), 2.0 (m, 1H, H-5$_{eq}$), 2.4–2.5 (m, 4H, $NCH_2CH_2CH_3$), 2.5–2.8 (m, 4H, H-4$_{eq,ax}$, H7$_{eq,ax}$), 3.09 (dddd, J=12.0, 11.0, 5.0, 2.0 Hz, 1H, H-6$_{ax}$), 5.96 (dd, J=2.5, 2.5 Hz, 1H, H-2), 6.63 (dd, J=2.5, 2.5 Hz, 1H, H-3), 7.77 (s, 1H, NH); ^{13}C NMR (90 MHz) δ 11.86 ($NCH_2CH_2CH_3$), 22.04 ($NCH_2CH_2CH_3$), 22.62 (C-4), 25.24 (C-7), 26.46 (C-5), 52.82 ($NCH_2CH_2CH_3$), 107.02 (C-3), 116.41 (C-2), 116.55 (C-3a), 126.26 (C-7a); EIMS 220 (M^+). Anal. Calcd for $C_{14}H_{24}N_2$ (220.36): C, 76.31; H, 10.98; N, 12.71. Found: C, 76.25; H, 10.84; N, 12.61. The enantiomer (*R*)-**26** was prepared as described for (*S*)-**26** using (*R*)-**24**: $[\alpha]_D^{20}=+53.9°$ (c=0.1, $CHCl_3$).

2.2. Receptor binding studies and mitogenesis experiments

To determine the binding affinities of the test compounds the human dopamine receptor subtypes D2$_{long}$, D2$_{short}$, D3 and D4.4, which were heterologously expressed in CHO cell lines, were employed in competition experiments together with the radioligand [^{3}H]spiperone (0.5 nM) and a series of 15 different concentrations of test compounds from 0.1 to 100,000 nM as triplicates according to literature.[19] Dopamine D1 affinities were established using porcine striatal membranes and the D1 selective radioligand [^{3}H]SCH23390 (0.3 nM). The resulting competition curves were analyzed by nonlinear regression analysis using the algorithms of PRISM (GraphPad Software, San Diego, CA) and the derived IC_{50} values were transformed into K_i values according to the equation of Cheng and Prusoff.[21] The resulting competition data were adjusted to mono- and biphasic curves. Considering statistic demands, a biphasic curve fitting was accepted when regression analysis coincidently indicated a rate of high affinity binding sites $>$ 20%. Otherwise, a monophasic curve was calculated. A mitogenesis assay with a D3 receptor expressing cell line was used to establish intrinsic activity according to the literature.[22] Stimulation of the receptor by an agonist or partial agonist test compound was measured an increase of [^{3}H]thymidine incorporation and compared to the full agonist quinpirole.

Acknowledgements

The authors thank Dr. J. -C. Schwartz and Dr. P. Sokoloff (INSERM, Paris), Dr. H. H. M. Van Tol (Clarke Institute of Psychiatry, Toronto) as well as Dr. J. Shine (The Garvan Institute of Medical Research, Sydney) for providing dopamine D3, D4 and D2 receptor expressing cell lines, respectively. Thanks are also due to Dr. R. Waibel for helpful discussions. This work was supported by the BMBF, and the Fonds der Chemischen Industrie.

References and notes

1. (a) Coppola, G. M.; Schuster, H. F. *Asymmetric synthesis*; Wiley: New York, 1987. (b) Gmeiner, P. In *Enantioselective synthesis of β-amino acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997; pp 67–81. (c) Gmeiner, P.; Feldman, P. L.; Chu-Moyer, M. Y.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3068.
2. (a) Gmeiner, P.; Kärtner, A.; Junge, D. *Tetrahedron Lett.* **1993**, *34*, 4325. (b) Gmeiner, P.; Kärtner, A. *Synthesis* **1995**, 83. (c) Weber, K.; Kuklinkski, S.; Gmeiner, P. *Org. Lett.* **2000**, *2*, 647. (d) Weber, K.; Ohnmacht, U.; Gmeiner, P. *J. Org. Chem.* **2000**, *65*, 7406.
3. (a) Gmeiner, P.; Junge, D.; Kärtner, A. *J. Org. Chem.* **1994**, *59*, 6766. (b) Gmeiner, P.; Mierau, J.; Höfner, G. *Arch. Pharm. (Weinheim)* **1992**, *325*, 57.
4. Lehmann, T.; Hübner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2863.
5. Lehmann, T.; Gmeiner, P. *Heterocycles* **2000**, *53*, 1371.
6. Michel, D.; Waibel, R.; Gmeiner, P. *Heterocycles* **1999**, *51*, 365.
7. (a) Andersen, K. E.; Braestrup, C.; Groenwald, F. C.; Joergensen, A. S.; Nielsen, E. B.; Sonnewald, U.; Soerensen, P. O.; Suzdak, P. D.; Knutsen, L. J. S. *J. Med. Chem.* **1993**, *36*, 1716. (b) Harrowven, D. C.; Dainty, R. F. *Tetrahedron Lett.* **1995**, *36*, 6739.
8. Lau, C. K.; Tardif, S.; Dufresne, C.; Scheigetz, J. *J. Org. Chem.* **1989**, *54*, 491.
9. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, *18*, 734.
10. Perri, S. T.; Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1986**, *51*, 3065.
11. (a) Hasan, I.; Marinelli, E. R.; Lin, L.-C. C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157. (b) Edwards, M. P.; Doherty, A. M.; Ley, S. V.; Organ, H. M. *Tetrahedron* **1986**, *42*, 3723.
12. Martinez, G. R.; Grieco, P. A.; Srinivasan, C. V. *J. Org. Chem.* **1981**, *46*, 3760.
13. Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Magolda, R. L.; Dolle, R. E. *J. Org. Chem.* **1985**, *50*, 1440.
14. Hobbs, C. F.; McMillin, C. K.; Papadopoulus, E. P.; Vander Werf, C. A. *J. Am. Chem. Soc.* **1962**, *84*, 43.
15. Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *J. Org. Chem.* **1990**, *55*, 6317.
16. (a) Bach, N. J.; Kornfeld, E. D.; Jones, N. D.; Chaney, M. O.; Dorman, D. E.; Paschal, J. W.; Clemens, J. A.; Smalstig, E. B. *J. Med. Chem.* **1980**, *23*, 481. (b) Bosch, J.; Roca, T.; Perez, C. G.; Montanari, S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 563.
17. Hayes, G.; Biden, T. J.; Selbie, L. A.; Shine, J. *Mol. Endocrinol.* **1992**, *6*, 920.
18. Sokoloff, P.; Andrieux, M.; Besançon, R.; Pilon, C.; Martres, M.-P.; Giros, B.; Schwartz, J.-C. *Eur. J. Pharmacol.* **1992**, *225*, 331.
19. Asghari, V.; Sanyal, S.; Buchwaldt, S.; Paterson, A.; Jovanovic, V.; Van Tol, H. H. M. *J. Neurochem.* **1995**, *65*, 1157.
20. Hübner, H.; Haubmann, C.; Utz, W.; Gmeiner, P. *J. Med. Chem.* **2000**, *43*, 756.
21. Cheng, Y. C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.
22. Hübner, H.; Kraxner, J.; Gmeiner, P. *J. Med. Chem.* **2000**, *43*, 4563.