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Enantiospecific synthesis and receptor binding of novel dopamine receptor ligands employing natural 4-hydroxyproline as a practical and flexible building block

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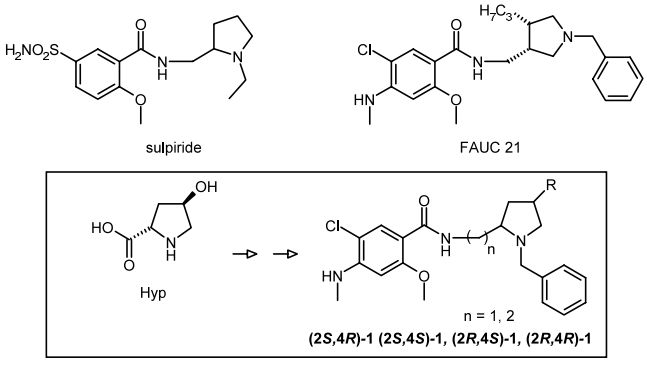
Abstract—Starting from natural 4-hydroxyproline, an ex-chiral pool approach is described giving access to 2-aminoalkylpyrrolidine derivatives that were used as chiral building blocks for the synthesis of bioactive 2-methoxybenzamide derivatives. The 4-hydroxy substituent can be displaced employing organocuprates as useful carbanion equivalents. Dopamine and serotonin binding studies involving the subtypes D1, $D2_{long}$, $D2_{short}$, D3 and D4 as well as 5-$HT1_A$ and 5-HT2, respectively, provided interesting insights into stereoselective structure activity relationships. The (2*S*,4*R*)-2-aminomethylpyrrolidine derivative ***ent*-66** and the (2*R*,4*S*)-2-aminoethylpyrrolidine derivative **68** showed remarkable affinity and preference for the dopamine D3 and D4 receptor subtypes, respectively, both being putatively associated to the symptoms of schizophrenia.

1. Introduction

In connection with our program on the development of atypical antipsychotic 2-methoxybenzamide derivatives,[1] we have reported a flexible approach to enantiomerically pure dopamine receptor ligands with 4-amino- and 4-aminomethylprolinol substructure when a practical ex-chiral pool synthesis starting from natural 4-hydroxyproline was employed.[2] Dopamine and serotonin receptor binding studies involving the subtypes D1, $D2_{long}$, $D2_{short}$, D3 and D4 as well as 5-$HT1_A$ and 5-HT2 displayed interesting structure activity relationships, especially with respect to the absolute and relative configuration of the test atoms within the diaminopropane substructure. In order to decrease D2 related extrapyramidal side-effects,[3] an extension of the study was envisioned involving a structural hybridization of the antipsychotic drug sulpiride and our previously developed D3 ligand FAUC 21.[4] We herein describe an ex-chiral pool synthesis of 2-aminomethyl-4-hydroxy-pyrrolidines as well as their 2-aminoethyl homologues starting from natural 4-hydroxyproline by exploiting chemo-, regio- and stereoselective functional group transformations at the 2- and 4-positions of the pyrrolidine moiety. Subsequent coupling reactions of these compounds with pharmacophoric 2-methoxybenzoic acid derivatives were performed leading to target compounds of type **1** in a variety of stereochemical configurations (Scheme 1). Finally, dopamine and serotonin receptor binding studies were done to gain insights into structure activity relationships, especially with respect to the stereochemistry of the test compounds.



Scheme 1.

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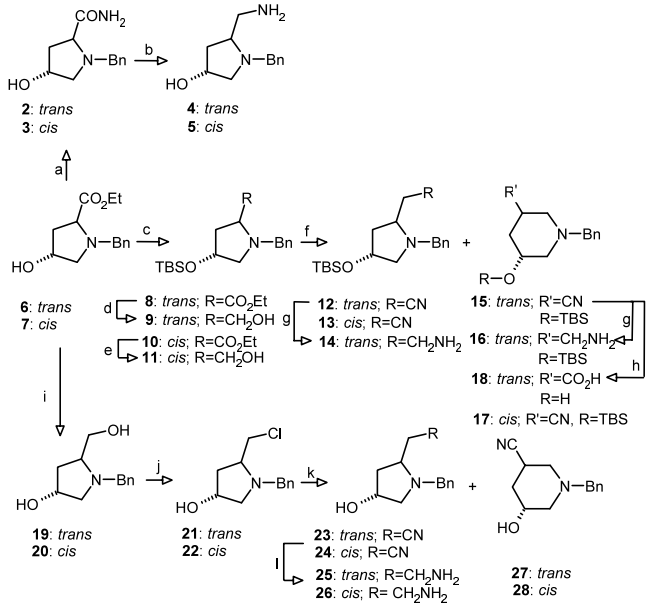
2. Synthesis

Our initial synthetic investigations were directed to the preparation of 2-aminomethyl- and 2-aminoethyl-4-hydroxypyrrolidines in all possible stereoisomeric forms when a benzyl group was utilized as a pharmacophoric unit directed at the pyrrolidine nitrogen. Our synthetic route involved chemo- and regioselective functional group transformations of 4-hydroxyproline derivatives using the readily available *trans*-substituted ethyl ester **6**, the corresponding diastereomeric ethyl ester **7** as well as the antipodes ***ent*-6** and ***ent*-7** as the central building blocks.[2] Two alternative synthetic pathways leading to *N*-benzyl-substituted 2-aminoethylpyrrolidine derivatives **14**, **25** and **26** were elaborated (Scheme 2).

Following the first strategy, the functionalization involved a temporary *O*-silylation of **6** and **7**.[5–9] Reduction of the thus obtained silylethers **8** and **10** with $LiAlH_4$ gave the primary alcohols **9** and **11**, respectively.[5,7] In the case of the *cis*-substituted derivative **10**, the reaction time had to be shortened to circumvent cleavage of the silylether function. Under these conditions the desired alcohol **11** was isolated only in moderate yield (26%) besides the diol **20**. Successive *O*-activation of the protected hydroxyproline-derivatives **9** and **11** and nucleophilic displacement using

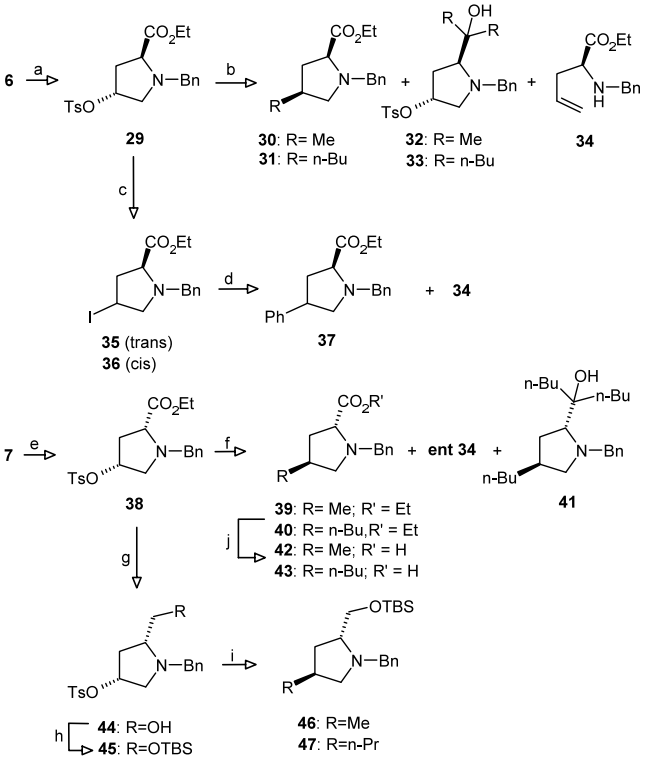


Scheme 2. *Reagents and conditions*: (a) NH_3 in MeOH, rt, 10 days (**2**: 98%, **3**: 98%); (b) $LiAlH_4$, Et_2O, reflux, 2 days (**4**: 95%, **5**: 89%); (c) **6**, TBSCl, imidazole, DMF, 0°C/3 h→rt/7 h (89%) or: **7**, TBSCl, imidazole, DMF, 0°C→rt/24 h (96%); (d) $LiAlH_4$, THF, 0°C, 2 h (99%); (e) $LiAlH_4$, THF, 0°C, 10 min (26%); (f) 1. NEt_3, Ms_2O, $CHCl_3$, 0°C, 3 h; 2. LiCN (0.5 M in DMF), 0°C→rt, 24 h (**12**: 51%, **15**: 18%, **13**/**17**: 84%); (g) $LiAlH_4$, Et_2O, 0°C, 2 h (**14**: 64%, **16**: 81%); (h) conc. HCl, reflux, 2 h (**18**×HCl: 99%); (i) $LiAlH_4$, THF, 0°C, 1 h (**19**: 98%, **20**: 98%); (j) $SOCl_2$, $CHCl_3$, reflux, 3.5 h (**21**×HCl: 74%, **22**×HCl: 80%); (k) NaCN, EtOH (80%), reflux, 24 h (**23**, **24**, **27**, 57%, **23**, **24**, **28**, 76%); (l) $LiAlH_4$, THF, 0°C, 1 h.

LiCN resulted in formation of the nitriles **12** and **13** in 51 and 70% yield, respectively.[2,7–12] During the synthesis that obviously proceeded through an aziridinium intermediate, rearrangement occurred giving the piperidine derivatives **15** and **17** as side products.[9,10,12–18] In the case of the *trans*-substituted derivatives, the pyrrolidine- and the piperidine-derivatives were formed in a 7:3 mixture of isomers. For the *cis*-isomers an 8:2 ratio was observed. Structural determination was performed by ^1H NMR and mass spectroscopy displaying diagnostic α-cleavage in the neighborhood of the amine nitrogens. Reduction of the carbonitriles **12** and **15** gave access to the primary amines **14** and **16**.[4] Following an alternative pathway renouncing temporary *O*-protection, selective functionalization[2,7–9,11] was accomplished by reduction of the ethyl esters **6** and **7**[2,12] and subsequent regiocontrolled activation of the primary alcohol functionality of the hydroxyprolinols **19** and **20** with $SOCl_2$ resulting in the formation of alkyl halides **21** and **22** that were isolated as analytically pure hydrochlorides in 74 and 80% yield, respectively.[19] Employing classical Kolbe conditions (NaCN, EtOH 80%, reflux)[13,18] crude **21** and **22** were transformed into the carbonitriles **23** and **24** besides minor amounts of the respective C-2 epimers and the rearrangement products **27** and **28**. $LiAlH_4$ promoted reduction of **23** and **24** afforded the aminoethyl substituted hydroxypyrrolidines **25** and **26** that were used in their crude form for coupling reactions with pharmacophoric methoxybenzoic acids. Preparation of the corresponding 2-aminomethyl derivatives **4** and **5** was also done starting from the precursors **6** and **7**, respectively, employing subsequent aminolysis and reduction.[6,20,21] The optical antipodes ***ent*-25**, ***ent*-26**, ***ent*-4** and ***ent*-5** were readily synthesized along the same reaction sequence starting from ***ent*-6** and ***ent*-7** in comparable yields. As an extension, the piperidine derivative **15** was transformed into the conformationally constrained GABA analogue **18** by refluxing **15** in concentrated HCl (99% yield).[22]

Bearing in mind that the hydrophobic effects played an important role in receptor binding, we tried to exchange the hydroxyl function at the 4-position of the pyrrolidine moiety by lipophilic alkyl substituents (Scheme 3).

For an EPC synthesis of 4-alkylpyrrolidines[23] we took advantage of our previously described displacement reactions at the 4-position of proline derivatives.[2] Starting from the secondary alcohol **7**, the introduction of nucleophiles was accomplished by *O*-sulfonylation and treatment of the intermediate **38** with organo cuprates (Me_2CuLi or Bu_2CuLi)[10,24–28] or Grignard reagents (MeMgBr, PrMgCl). Employing Gilman cuprates, the success of the synthesis of the 4-alkyl substituted derivatives **39** and **40** was strongly dependent on the amount of nucleophile used for the reaction. For the preparation of the 4-methyl derivative **39**, 7 equivalents of the cuprate reagent (Me_2CuLi) resulted in formation of the desired product in 70% yield. The ester function was preserved under these reaction conditions. Epimerization at the 2-position could not be observed. On the other hand, the use of 7 equivalents of Bu_2CuLi under



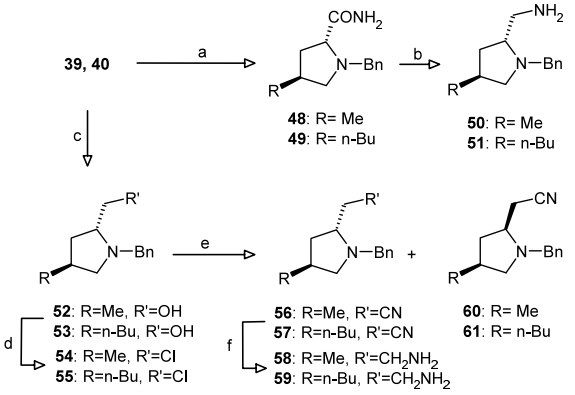
Scheme 3. *Reagents and conditions*: (a) Ref. 2; (b) Me_2CuLi (7 equiv.), Et_2O, 0°C, 2 h (**30**: 11%, **32**: 55%); Li_2CuCl_4, MeMgBr, THF, 0°C, 3 h (**32**: 86%); *n*-Bu_2CuLi (1.8 equiv.), Et_2O, –20°C, 2 h (**31**: 24%) or: *n*-Bu_2CuLi (11 equiv.), Et_2O, –20°C, 3.5 h (**31**: 45%) or *n*-$Bu_2CuCNLi_2$ (1 equiv.), Et_2O, –40°C, 3 h (**33**: 80%), (c) NaI, acetone, reflux, 48 h (**35**/**36**: 97%); (d) **35**/**36**, Zn, DMF, $Pd_2(dba)_3$, P(*o*-Tol)$_3$, C_6H_5I, rt, 24 h (**37**: 55%) or: **36**, Zn, DMF, $Pd_2(dba)_3$, P(*o*-Tol)$_3$, C_6H_5I, rt, 24 h (**34**: 94%); (e) Ref. 2; (f) Me_2CuLi (7 equiv.), Et_2O, 0°C, 1.5 h (**39**: 70%) or: *n*-Bu_2CuLi (1.8 equiv.), Et_2O, –20°C, 2 h (**40**: 74%) or: Bu_2CuLi (7 equiv.), Et_2O, –20°C, 1 h (**41**: 74%); (g) $LiAlH_4$, THF, 0°C, 1 h (92%); (h) TBSCl, imidazole, DMF, 0°C→rt, 24 h (95%); (i) MeMgBr, Et_2O, 0°C, 90 min→rt, 5 h (**46**: 75%); *n*-PrMgCl, Et_2O, 0°C/90 min→rt/3 h (**47**: 79%); (j) 5 M HCl, 60°C, 48 h (**42**×HCl, **43**×HCl, 99%).

identical conditions gave nucleophilic attack at both possible reaction centers resulting in the formation of 74% of the tertiary alcohol **41**. Reducing the amount of Bu_2CuLi to 1.8 equivalents, **40** was synthesized in 74% yield along with the protected allylglycine ***ent*-34** as a side product that is obviously formed by metallation and subsequent β-elimination. NOE experiments clearly established the *trans*-configuration of **39** and **40** and thus the S_N2-type character of the coupling reaction. Hydrolylsis of the ethyl ester functions gave the *N*-protected 4-alkylprolines **42** and **43**. Starting from the building block ***ent*-7**, the optical antipodes ***ent*-42** and ***ent*-43** could be prepared under identical reaction conditions. In order to investigate the stereochemical integrity of the reaction sequence, HPLC analysis on a chiral stationary phase was performed indicating an enantiomeric purity of >99%.

The synthesis of the *cis*-diastereomers **30** and **31** was performed starting from the tosylate **29** which was readily available from the hydroxyprolinate **6**. Treatment of **29** with 7 equivalents of Me_2CuLi obtained the desired 4-methylproline derivative **30** in only 11% yield along with the tertiary alcohol **32** as the main product (55%). For the synthesis of the 4-butylproline **31**, we initially employed 1.8 equivalents of Bu_2CuLi as applied for the synthesis of the *trans*-derivative **40** when 24% of the desired *cis*-4-butyl-derivative **31** was isolated. As already observed for the *trans*-derivatives, a reductive elimination occurred giving 34% of the ring-opened derivative **34**. Increasing the amount of Gilman reagent to 11 equivalents, 45% of **31** was obtained. Cyanocuprates[28–31] or the use of Kochi's catalyst[32–34] proved not to be advantageous for the synthesis of the *cis*-substituted derivatives since selective attack at the carboxylate function occurred, affording **32** or **33** in 80–86% yield, respectively. Reacting organomagnesium cuprates[28,31,35,36] with the tosylates **29** and **38** furnished the iodides and **36** and ***ent*-35**, respectively, with complete inversion. Starting from the *trans*-substituted tosylate **29**, we succeeded in a phenylation by organozinc reagents.[37–40] In order to create a suitable leaving group for a Negishi coupling,[41] replacement of the tosyl function by an iodo-substituent[42] was performed upon refluxing **29** and NaI in acetone to give a diastereomeric mixture of the iodides **35** and **36**, which were then separated by flash chromatography. NOE experiments established the inversion of stereochemistry at the 4-position during the displacement reactions. Metalation of **35** and **36** with Zn and subsequent palladium assisted coupling with iodobenzene resulted in formation of the 4-phenylpyrrolidine **37** as a mixture of diastereomers in 55% yield besides the ring-opening product **34**.[37–40] Interestingly, exclusive formation of the protected allylglycine **34** in 94% yield was accomplished when reacting only the *cis*-diastereomer **36** under identical reaction conditions. To circumvent the problem of chemoselectivity during the nucleophilic attack, the displacement reaction at the 4-position was performed after reducing the carboxylate function at the 2-position. Thus, the ethyl ester **38** was reacted with $LiAlH_4$ to afford the primary alcohol **44** (92%).[5,7] Subsequent *O*-protection[5–9] using TBSCl in the presence of imidazole gave access to the protected tosylate **45** in 95% yield, which was readily transformed to the protected 4-alkylpyrolinol derivatives **46** and **47** upon treatment of **45** under Grignard reaction conditions with MeMgBr and PrMgCl, respectively.

Further functional group transformations at the 2-position of the pyrrolidine moiety of the 4-alkylproline derivatives **39** and **40** led to the respective 2-aminomethyl- and aminomethylpyrrolidines **50**, **58** and **51**, **59**, respectively, as shown in Scheme 4.

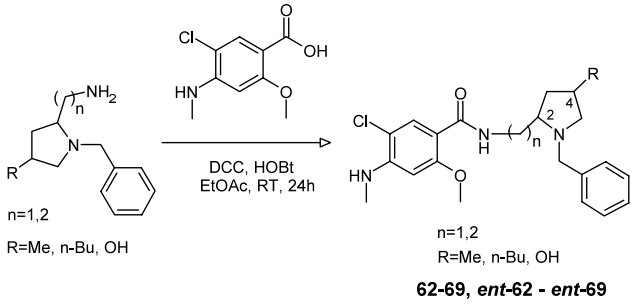
In particular, the reactive intermediates **54** and **55** were synthesized from **39** and **40** by $LiAlH_4$-reduction[5,7] and activation of the resulting primary alcohols **52** or **53** by $SOCl_2$.[20] Nucleophilic displacement of crude **54** and **55** under Kolbe conditions[13,18] resulted in the formation of the nitriles **56** and **57** in high overall yield along with



Scheme 4. *Reagents and conditions*: (a) NH_3, MeOH, rt, 10 days (**48**: 94%, **49**: 66%); (b) $LiAlH_4$, Et_2O, reflux, 24 h (**50**: 85%, **51**: 96%); (c) $LiAlH_4$, THF, 0°C, 30–60 min, (**52**: 92%, **53**: 98%); (d) $SOCl_2$, $CHCl_3$, reflux, 4–24 h; (e) **54** or **55**, $SOCl_2$, $CHCl_3$, reflux, 4 h; (e) NaCN, EtOH (80%), reflux, 24–48 h (49–72%); (f) $LiAlH_4$, THF, 0°C, 1 h.

the *cis*-epimers **60** and **61**. Finally, reduction of the carbonitriles **56** and **57** afforded the primary amines **58** and **59**, respectively. Preparation of the corresponding aminomethylpyrrolidines **50** and **51** was accomplished starting from **39** or **40** by aminolysis of the ester function and further reduction.[6,19,21] The antipodes ***ent*-50**, ***ent*-51** as well as their homologues ***ent*-58** and ***ent*-59** were synthesized along the same sequence starting from ***ent*-39** and ***ent*-40**.

For the synthesis of the target compounds of type **1**, DCC/HOBt promoted coupling of the amines **25**, **26**, **4**, **5**, **58** and **59** as well as their antipodes ***ent*-25**, ***ent*-26**, ***ent*-4**, ***ent*-5**, ***ent*-58** and ***ent*-59** to 5-chloro-2-methoxy-4-methylaminobenzoic acid gave access to the 2-methoxybenzamides **62–69** as well as to their antipodes ***ent*-62**–***ent*-69**, respectively (Scheme 5).



Scheme 5.

3. Pharmacology

The novel methoxybenzamide derivatives were evaluated in vitro with respect to their binding affinities and receptor subtype selectivities by radioligand binding assays for the dopamine receptors D1–D4[43–46] and for the serotonin receptors 5-$HT1_A$ and 5-HT2. Affinities for the D1 receptor were determined by employing bovine striatal membranes and the selective antagonist [^{3}H]SCH 23390 as a radioligand.[46] Binding studies on the subtypes of the D2 family were performed using membrane preparations of CHO cells stably expressing the human dopamine receptors $D2_{long}$, $D2_{short}$,[43] D3[44] and D4.4[45] and [^{3}H]spiperone as the radioligand. Since both dopamine and serotonin receptors play an important part in psychotic disorders and some methoxybenzamides are known for their serotoninergic properties,[47] 5-HT-binding was also investigated employing porcine cortical membrane preparations and the radioligands [^{3}H]8-OH-DPAT and [^{3}H]ketanserin for 5-$HT1_A$ and 5-HT2, respectively. The antipsychotic drug sulpiride and the D3 receptor preferring ligand FAUC 21 were utilized as reference compounds. The results are presented in Table 1 (K_i values in nM as means of two to three competition experiments). Binding data provided interesting results concerning the binding affinity and receptor subtype selectivity with respect to the substitution pattern and the stereochemical entities of the pyrrolidine moiety. In particular, the aminomethylpyrrolidine derivatives **62**, **63**, ***ent*-62** and ***ent*-63** displayed substantial affinities to the subtypes of the D2 family including $D2_{long}$, $D2_{short}$, D3 and D4.4. In contrast, the aminoethyl substituted homologues showed only modest receptor binding indicating, as already observed for our previously developed nemonapride analogues,[2] that the distance between the basic pyrrolidine nitrogen and the methoxybenzamide functionality as the major pharmacophoric elements is crucial for the receptor recognition. With regard to the aminomethylpyrrolidine derivatives, the (2*R*)-configured isomers showed substantially higher binding affinities compared to the (2*S*)-stereoisomers. Among the (2*R*)-isomers, the (2*R*,4*S*)-derivative **63** displayed high binding affinity but poor subtype selectivity. Compared to the 4-hydroxy-substituted derivatives, the binding affinities of the 4-alkylpyrrolidines were generally higher. Looking at the *trans*-substituted derivatives, the 4-methyl substituted target compound ***ent*-66** displayed high D3 affinity with a K_i value of 20 nM and a selectivity pattern of 700, 17, 14, 73, 37 and 150 when compared to D1 (K_i = 14000 nM), $D2_{long}$ (K_i = 330 nM), $D2_{short}$ (K_i = 280 nM), D4 (K_i = 1500 nM), 5HT1A (K_i = 740 nM) and 5HT2 (K_i = 3000 nM), respectively. In comparison to sulpiride, an increased D3/D4- and D2/D3-selectivity was noticed for ***ent*-66**. The (2*R*,4*S*)-configured 4-butylpyrrolidine **68** displayed high D4 affinity with a K_i value of 8 nM and a selectivity of 118, 275 and 200, when compared to D3 (K_i = 945 nM), 5HT1A (K_i = 2200 nM) and 5HT2 (K_i = 1600 nM), but with low selectivity (4,3), when compared to $D2_{long}$ (K_i = 35 nM) and $D2_{short}$ (K_i = 21 nM).

In conclusion, chirospecific transformations of hydroxyproline derivatives led to a number of bioactive methoxybenzamides displaying receptor binding profiles that proved strongly dependant on the absolute and relative configuration of the test compounds.

Table 1. Binding affinities of the methoxybenzamides **62–69**, ***ent*-62–*ent*-69** and the reference compounds sulpiride and FAUC 21 to the bovine dopamine D1, the human $D2_{long}$, $D2_{short}$, D3 and D4.4 as well as to the porcine 5-$HT1_A$ and 5-HT2 receptors

Compound	R	Pos. 2	Pos. 4	*n*	K_i values [nM][a]						
					[^{3}H]SCH23390	[^{3}H]Spiperone				[^{3}H]8-OH-DPAT	[^{3}H]Ketanserin
					D1	$D2_{long}$	$D2_{short}$	D3	D4.4	5-$HT1_A$	5-HT2
62	OH	*R*	*R*	1	12000	500	480	430	120	1300	2400
***ent*-62**	OH	*S*	*S*	1	3600	440	1300	500	2500	2600	3100
63	OH	*R*	*S*	1	11000	19	14	29	42	410	530
***ent*-63**	OH	*S*	*R*	1	14000	1800	2100	510	40000	5100	9000
64	OH	*R*	*S*	2	14000	320	190	1300	100	2400	1200
***ent*-64**	OH	*R*	*S*	2	28000	2900	2000	8600	8400	8200	15000
65	OH	*S*	*S*	2	14000	2700	2000	2400	1100	3000	4800
***ent*-65**	OH	*R*	*R*	2	62000	5300	3800	20000	21000	2500	15000
66	Me	*R*	*S*	1	6700	67	42	140	800	1800	2300
***ent*-66**	Me	*S*	*R*	1	14000	330	280	20	1500	740	3000
67	*n*-Bu	*R*	*S*	1	930	230	92	67	260	850	3100
***ent*-67**	*n*-Bu	*S*	*R*	1	7200	230	120	52	1000	1600	2900
68	Me	*R*	*S*	2	16000	35	21	950	8.0	2200	1600
***ent*-68**	Me	*S*	*R*	2	17000	530	600	1600	370	650	2200
69	*n*-Bu	*R*	*S*	2	2400	24	15	540	160	3700	3800
***ent*-69**	*n*-Bu	*S*	*R*	2	7000	140	96	310	130	1400	1600
Sulpiride					50000	120	51	88	2100	9800	4300
FAUC 21					2800	190	190	31	200	n.d.	n.d.

[a] K_i value in [nM] are the means of two to three competition experiments each done in triplicate.

4. Experimental

4.1. General procedures

Et_2O, THF and toluene were distilled from Na, $CHCl_3$, CH_2Cl_2 from CaH_2, and EtOH from Mg immediately before use. Dry DMF, DMSO and dry pyridine were purchased from FLUKA. All liquid reagents were purified by distillation. All reactions were conducted under anhydrous N_2. Evaporation of the final product solution was performed under vacuum with a rotatory evaporator. Flash chromatography was carried out with 230–400 mesh silica gel. Melting points: Büchi melting point apparatus, uncorrected. IR spectra: PERKIN–ELMER FT/IR 241 or Jasco FT/IR 410 spectrometer. Mass spectra: FINNIGAN MAT TSQ 70 instrument. High resolution mass spectrometry: FINNIGAN MAT 8200. ^{1}H NMR and ^{13}C NMR spectra: BRUKER AM 360 spectrometer at 360 and 90 MHz. Spectra were measured in $CDCl_3$ using TMS as an internal standard. Optical rotations were measured at 23°C with a PERKIN–ELMER 241 polarimeter. Elementary analyses were performed by the Organic Chemistry Department of the Friedrich-Alexander-University Erlangen-Nürnberg or by Beetz Microanalysis Laboratory, Kronach, Germany. For all new compounds satisfactory microanalyses were obtained C±0.39, H±0.17, N±0.29, S±0.13.

4.2. (2*S*,4*R*)-1-Benzyl-4-hydroxypyrrolidine-2-carboxamide 2

A solution of **6**[2] (1.098 g, 4.4 mmol) and MeOH saturated with NH_3 (30 mL) at −20°C were allowed to warm up to rt and stirred for 10 days. The solvent was then removed under reduced pressure to give pure **2** (0.95 g, 98%) as a yellowish, crystalline solid. Mp: 39°C; EI-MS $m/z = 220$ [M^+]; TLC: $R_f = 0.17$ (CH_2Cl_2/MeOH = 95:5); IR (film): ν 3421, 1670, 1454, 1333, 1127, 1082, 735, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 2.10 (ddd, 1H, $J = 13.4$, 8.2, 6.6 Hz, H-3a), 2.25 (ddd, 1H, $J = 13.4$, 8.2, 4.2 Hz, H-3b), 2.48 (dd, 1H, $J = 10.6$, 4.5 Hz, H-5a), 3.30 (dd, 1H, $J = 10.6$, 5.5 Hz, H-5b), 3.54 (dd, 1H, $J = 8.2$, 8.2 Hz, H-2), 3.63 (d, 1H, $J = 13.0$ Hz, NCH_2Ph), 3.98 (d, 1H, $J = 13.0$ Hz, NCH_2Ph), 4.41 (m, 1H, H-4), 5.54 (brs, 1H, NH_2), 7.13 (brs, 1H, NH_2), 7.24–7.38 (m, 5H, Ar); Anal. calcd for $C_{12}H_{16}N_2O_2$ (220.27): C, 65.43; H, 7.32; N, 12.72, found: C, 65.44; H, 7.26; N, 12.79; $[\alpha]_D^{20} = -79.6$ (*c* 1.0, $CHCl_3$).

***ent*-2**[21] was prepared under the same reaction conditions as described for **2**, starting from ***ent*-6**; $[\alpha]_D^{20} = +76.5$ (*c* 1.0, $CHCl_3$).

4.3. (2*R*,4*R*)-1-Benzyl-4-hydroxypyrrolidine-2-carboxamide 3

A mixture of **7** (725 mg, 2.9 mmol) and sat. NH_3/MeOH (20 mL) was reacted and worked up as

described for **2** to give pure **3** (627 mg, 98%) as a yellow solid. Mp: 78–79°C; EI-MS $m/z=220$ [M^+]; TLC: $R_f=0.30$ (CH_2Cl_2/MeOH = 9:1); IR (film): ν 3418, 1668, 1453, 1311, 1124, 1085, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 1.99 (brdd, 1H, $J=14.2$, 4.5 Hz, H-3a), 2.51 (m, 2H, H-3b/H-5a), 3.04 (brd, 1H, $J=10.3$ Hz, H-5b), 3.24 (dd, 1H, $J=10.8$, 4.5 Hz, H-2), 3.53 (d, 1H, $J=13.0$ Hz, NCH_2Ph), 3.96 (d, 1H, $J=13.0$ Hz, NCH_2Ph), 4.34 (m, 1H, H-4), 7.39–7.17 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 62.90 MHz): δ 39.97 (C-3), 59.27 (NCH_2Ph), 61.54 (C-5), 66.02 (C-2), 70.73 (C-4), 127.42, 128.51, 128.78, 137.89 (C-Ar), 177.89 ($\underline{C}ONH_2$); Anal. calcd for $C_{12}H_{16}N_2O_2$ (220.27): C, 65.43; H, 7.32; N, 12.72, found: C, 65.48; H, 7.39; N, 12.65; $[\alpha]_D^{20}=+39.6$ (c 1.0, $CHCl_3$).

***ent*-3** was prepared under the same reaction conditions as described for **3**, starting from ***ent*-7**; $[\alpha]_D^{20}=-42.9$ (c 0.9, $CHCl_3$).

4.4. (3*R*,5*S*)-5-Aminomethyl-1-benzylpyrrolidin-3-ol 4

To a stirred solution of **2** (48.5 mg, 0.22 mmol) in Et_2O (10 mL) was added $LiAlH_4$ (0.88 mL, 1 M solution in Et_2O) and the resulting mixture left to reflux for 2 days. After cooling to rt, the mixture was worked up as described for **19** (extraction was performed with MeOH, eluent for flash chromatography: CH_2Cl_2/MeOH = 8:2+3 mL of NH_3-saturated MeOH) to leave pure **4**[21] (43.2 mg, 95%) as a colorless crystalline solid. Mp: 157–158°C; CI-MS $m/z=207$ [M+1$^+$]; TLC: $R_f=0.18$ (CH_2Cl_2/MeOH = 8:2+3 mL of NH_3-saturated MeOH/500 mL eluent); IR (film): ν 3352, 1572, 1453, 1331, 1122, 1027, 743, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 1.83 (ddd, 1H, $J=13.2$, 7.8, 4.0 Hz, H-4a), 2.02 (ddd, 1H, $J=13.2$, 7.7, 7.6 Hz, H-4b), 2.34 (dd, 1H, $J=10.4$, 4.8 Hz, H-2a), 2.75 (dd, 1H, $J=13.1$, 2.9 Hz, $C\underline{H}_2NH_2$), 2.83 (dd, 1H, $J=13.1$, 5.0 Hz, $C\underline{H}_2NH_2$), 2.99 (m, 1H, H-5), 3.29 (dd, 1H, $J=10.4$, 5.6 Hz, H-2b), 3.47 (d, 1H, $J=13.1$ Hz, NCH_2Ph), 4.03 (d, 1H, $J=13.1$ Hz, NCH_2Ph), 4.38 (m, 1H, H-3), 7.19–7.38 (m, 5H, Ar); HR-EIMS: 176.10749 (Anal. calcd for $C_{11}H_{14}NO$: 176.10754), 188.13138 (Anal. calcd for $C_{12}H_{16}N_2$: 188.13135); $[\alpha]_D^{20}=-54.6$ (c 1.0, $CHCl_3$).

***ent*-4** was prepared under the same reaction conditions as described for **4**, starting from ***ent*-2**; $[\alpha]_D^{20}=+57.1$ (c 0.04, $CHCl_3$).

4.5. (3*R*,5*R*)-5-Aminomethyl-1-benzylpyrrolidin-3-ol 5

A solution of **3** (291 mg, 1.32 mmol) in Et_2O (5 mL) and $LiAlH_4$ (5.3 mL, 1 M solution in Et_2O) was reacted and worked up (CH_2Cl_2/MeOH = 8:2+6 mL of NH_3-saturated MeOH/500 mL eluent) as described for **4** to give pure **5** (242.8 mg, 89%) as a yellow oil; EI-MS $m/z=176$ (α-cleavage, [M−CH_2NH_2]$^+$); TLC: $R_f=0.17$ (CH_2Cl_2/MeOH = 8:2+6 mL of NH_3-saturated MeOH/500 mL eluent); IR (film): ν 3363, 3061–2793, 1584, 1453, 1340, 1126, 1026, 969, 738, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 1.64 (brd, 1H, $J=13.7$ Hz, H-3a), 2.31 (m, 2H, H-3b/H-5a), 2.45 (dd, 1H, $J=9.7$, 3.1 Hz, $C\underline{H}_2NH_2$), 2.64 (dd, 1H, $J=12.5$, 3.3 Hz, H-5b), 2.98 (m, 2H, $C\underline{H}_2NH_2$/H-2), 3.62 (d, 1H, $J=13.4$ Hz, NCH_2Ph), 3.82 (d, 1H, $J=13.4$ Hz, NCH_2Ph), 4.09 (m, 1H, H-4), 7.19–7.33 (m, 5H, Ar); HR-EIMS: 176.10783 (Anal. calcd for $C_{11}H_{14}NO$: 176.10754); $[\alpha]_D^{20}=+30.3$ (c 1.0, $CHCl_3$).

***ent*-5** was prepared under the same reaction conditions as described for **5**, starting from ***ent*-5**; $[\alpha]_D^{20}=-21.6$ (c 0.08, $CHCl_3$).

4.6. Ethyl (2*S*,4*R*)-1-benzyl-4-(*tert*-butyldimethylsilyloxy)prolinate 8

To a solution of **6** (1.6 g, 6.2 mmol) in DMF (250 mL) was added imidazole (1.3 g, 18.7 mmol) and TBSCl (1.4g, 9.4 mmol) at 0°C. After stirring at 0°C for 3 h, the mixture was allowed to warm up to rt and stirring continued for another 7 h. An aqueous saturated solution of NH_4Cl was then added and the reaction mixture extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc = 7:3) to give **8** (2.0 g, 89%) as a colorless oil; EI-MS $m/z=363$ [M^+] TLC: $R_f=0.69$ (petroleum ether/EtOAc = 1:1); IR (film): ν 3086–2801, 1747, 1471, 1375, 1255, 1181, 1096, 1031, 835, 776, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.02 (s, 6H, $OSi(C\underline{H}_3)_2t$Bu), 0.09 (s, 9H, $OSi(CH_3)_2t\underline{Bu}$), 1.23 (t, 3H, $J=7.0$ Hz, $CO_2CH_2C\underline{H}_3$), 2.01 (ddd, 1H, $J=12.9$, 8.2, 4.3 Hz, H-3a), 2.17 (ddd, 1H, $J=12.9$, 7.8, 7.4 Hz, H-3b), 2.34 (dd, 1H, $J=9.7$, 5.1 Hz, H-5a), 3.23 (dd, 1H, $J=9.7$, 5.7 Hz, H-5b), 3.49 (dd, 1H, $J=8.2$, 7.8 Hz, H-2), 3.56 (d, 1H, $J=12.7$ Hz, NCH_2Ph), 3.92 (d, 1H, $J=12.7$ Hz, NCH_2Ph), 4.10 (m, 2H, $CO_2C\underline{H}_2CH_3$), 4.39 (m, 1H, H-4), 7.20–7.34 (m, 5H, Ar); Anal. calcd for $C_{20}H_{33}NO_3Si$ (363.58): C, 66.07; H, 9.15; N, 3.85, found: C, 65.69; H, 9.31; N, 3.81; $[\alpha]_D^{20}=-41.0$ (c 1.0, $CHCl_3$).

***ent*-8** was prepared under the same reaction conditions as described for **8**, starting from ***ent*-6**; $[\alpha]_D^{20}=+38.8$ (c 1.0, $CHCl_3$).

4.7. (3*R*,5*S*)-1-Benzyl-3-(*tert*-butyldimethylsilyloxy)-5-hydroxymethylpyrrolidine 9

A mixture of **8** (1.2 g, 3.4 mmol) and $LiAlH_4$ (6.6 mL, 1 M solution in THF) in THF (30 mL) was reacted for 2 h and worked up (extraction with Et_2O instead of CH_2Cl_2) as described for **19** to leave pure **9**[12] (1.1 g, 99%) as yellowish crystals. Mp: 37°C; EI-MS $m/z=290$ (α-cleavage, [M−CH_2OH]$^+$); TLC: $R_f=0.14$ (petroleum ether/EtOAc = 1:1); IR (film): ν 3428, 3063–2856, 1471, 1254, 1111, 1051, 835, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.02 (s, 6H, $OSi(C\underline{H}_3)_2t$Bu), 0.86 (s, 9H, $OSi(CH_3)_2t\underline{Bu}$), 1.81 (ddd, 1H, $J=13.5$, 8.4, 4.6 Hz, H-4a), 2.05 (ddd, 1H, $J=13.5$, 13.2, 6.7 Hz, H-4b), 2.35 (dd, 1H, $J=9.8$, 5.7 Hz, H-2a), 3.04 (m, 1H, H-5), 3.12 (dd, 1H, $J=9.8$, 5.5 Hz, H-2b), 3.37 (dd, 1H, $J=11.0$, 1.7 Hz, CH_2OH), 3.46 (d, 1H, $J=13.0$, NCH_2Ph), 3.63 (dd, 1H, $J=11.0$, 3.4 Hz, CH_2OH), 3.95 (d, 1H, $J=13.0$, NCH_2Ph), 4.25 (m, 1H, H-3), 7.20–7.36 (m, 5H, Ar); $[\alpha]_D^{20}=-36.5$ (c 1.0, $CHCl_3$).

***ent*-9** was prepared under the same reaction conditions as described for **9**, starting from ***ent*-8**; $[\alpha]_D^{20} = +38.6$ (*c* 1.0, $CHCl_3$).

4.8. Ethyl (2*R*,4*R*)-1-benzyl-4-(*tert*-butyldimethylsilyloxy)prolinate 10

A solution of **7** (10.8 g, 43.4 mmol) in DMF (200 mL), imidazole (8.9 g, 130.2 mmol) and TBSCl (9.79 g, 65.0 mmol) was reacted and worked up (eluent for flash chromatography: petroleum ether/EtOAc = 1:1) as described for **8** to give **10** (15.1 g, 96%) as a colorless oil; EI-MS $m/z = 363$ [M^+]; TLC: $R_f = 0.61$ (petroleum ether/EtOAc = 6:4); IR (film): ν 2954–2856, 1741, 1471, 1253, 1181, 1098, 835, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.01 (s, 6H, $OSi(C\underline{H}_3)_2tBu$), 0.75 (s, 9H, $OSi(CH_3)_2t\underline{Bu}$), 1.27 (t, 3H, $J = 7.0$ Hz, $CO_2CH_2C\underline{H}_3$), 1.98 (ddd, 1H, $J = 12.8$, 7.5, 5.1 Hz, H-3a), 2.41 (ddd, 1H, $J = 12.8$, 7.5, 7.5 Hz, H-3b), 2.70 (dd, 1H, $J = 9.9$, 6.5 Hz, H-5a), 2.94 (dd, 1H, $J = 9.9$, 3.8 Hz, H-5b), 3.34 (dd, 1H, $J = 7.5$, 7.5 Hz, H-2), 3.62 (d, 1H, $J = 13.4$ Hz, NCH_2Ph), 3.98 (d, 1H, $J = 13.4$ Hz, NCH_2Ph), 4.16 (m, 2H, $CO_2C\underline{H}_2CH_3$), 4.35 (m, 1H, H-4), 7.19–7.38 (m, 5H, Ar); Anal. calcd for $C_{20}H_{33}NO_3Si$ (363.58): C, 66.07; H, 9.15; N, 3.85, found: C, 66.13; H, 9.04; N, 3.71; $[\alpha]_D^{20} = +42.0$ (*c* 1.0, $CHCl_3$).

***ent*-10** was prepared under the same reaction conditions as described for **10**, starting from ***ent*-7**; $[\alpha]_D^{20} = -38.5$ (*c* 1.0, $CHCl_3$).

4.9. (3*R*,5*R*)-1-Benzyl-3-(*tert*-butyldimethylsilyloxy)-5-hydroxymethylpyrrolidine 11 and (3*R*,5*R*)-1-benzyl-5-hydroxymethylpyrrolidin-3-ol 20

A mixture of **10** (3.09 g, 8.49 mmol) and $LiAlH_4$ (12.7 mL, 1 M solution in THF) in THF (50 mL) was reacted for 10 min and worked up (petroleum ether/EtOAc = 75:25) as described for **20** to leave pure **11** (874 mg, 32%) as a weakly yellowish oil; EI-MS $m/z = 321$ [M^+]; 290 (α-cleavage, [$M-CH_2OH$]$^+$); TLC: $R_f = 0.41$ (petroleum ether EtOAc = 1:1); IR (film): ν 3443, 3027–2793, 1471, 1254, 1052, 835, 776, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.04 (s, 6H, $OSi(C\underline{H}_3)_2tBu$), 0.88 (s, 9H, $OSi(CH_3)_2t\underline{Bu}$), 1.87 (ddd, 1H, $J = 13.6$, 5.2, 3.9 Hz, H-4a), 2.21 (ddd, 1H, $J = 13.6$, 9.6, 5.8 Hz, H-4b), 2.43 (dd, 1H, $J = 9.9$, 4.5 Hz, H-2a), 2.88 (m, 2H, H-2b/H-5), 3.41 (d, 1H, $J = 13.4$ Hz, NCH_2Ph), 3.45 (brd, 1H, $J = 10.6$ Hz, $C\underline{H}_2OH$), 3.72 (brd, 1H, $J = 10.6$ Hz, $C\underline{H}_2OH$), 4.02 (d, 1H, $J = 13.4$ Hz, NCH_2Ph), 4.26 (m, 1H, H-3), 7.21–7.40 (m, 5H, Ar); Anal. calcd for $C_{18}H_{31}NO_2Si$ (321.54): C, 67.24; H, 9.72; N, 4.36, found: C, 67.36; H, 9.85; N, 4.37; $[\alpha]_D^{20} = +46.2$ (*c* 1.0, $CHCl_3$).

Compound **20** can also be isolated in pure form (1.105 g, 63%), too, when the eluent is changed to CH_2Cl_2/MeOH = 9:1.

***ent*-11** and ***ent*-20** were prepared under the same reaction conditions as described for **11** and **20**, starting from ***ent*-10**.

Additional analytical data of ***ent*-11**: $[\alpha]_D^{20} = -45.9$ (*c* 1.0, $CHCl_3$).

4.10. (2*S*,4*R*)-[1-Benzyl-4-(*tert*-butyldimethylsilyloxy)-pyrrolidin-2-yl]acetonitrile 12 and (3*R*,5*R*)-1-benzyl-5-(*tert*-butyldimethylsilyloxy)piperidine-3-carbonitrile 15

To a solution of **9** (338 mg, 1.1 mmol) in $CHCl_3$ (15 mL) was added NEt_3 (0.04 mL, 0.29 mmol) and Ms_2O (41.8 mg, 0.2 mmol) at 0°C. After 3 h of stirring at 0°C, a cold solution of LiCN (4 mL, 0.5 M in DMF) was added. Then, the mixture was allowed to warm up to rt and stirring continued for another 24 h. An aqueous saturated solution of Na_2CO_3 was added and the mixture extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc = 95:5 and successive gradient eluent: pure petroleum ether, petroleum ether/EtOAc = 95:5 to 8:2) to give **12** (179 mg, 51%) and **15** (63.1 mg, 18%) as a white solid, respectively.

Analytical data of **12**: Mp: 26–30°C; EI-MS $m/z = 330$ [M^+], 290 (α-cleavage, [$M-CH_2CN$]$^+$); TLC: $R_f = 0.19$ (petroleum ether/EtOAc = 9:1); IR (film): ν 3027–2856, 2247, 1471, 1360, 1255, 1101, 836, 777, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.02 (s, 3H, $OSi(C\underline{H}_3)_2tBu$), 0.04 (s, 3H, $OSi(C\underline{H}_3)_2tBu$), 0.87 (s, 9H, $OSi(CH_3)_2C(C\underline{H}_3)_3$), 1.9 (m, 2H, H-3a/H-3b), 2.33 (dd, 1H, $J = 10.0$, 4.8 Hz, H-5a), 2.41 (m, 2H, CH_2CN/CH_2CN), 3.13 (m, 1H, H-2), 3.21 (dd, 1H, $J = 10.0$, 5.7 Hz, H-5b), 3.53 (d, 1H, $J = 13.1$ Hz, NCH_2Ph), 3.92 (d, 1H, $J = 13.1$ Hz, NCH_2Ph), 4.36 (m, 1H, H-4), 7.21–7.37 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 62.90 MHz): δ 17.96 ($OSi(\underline{C}H_3)_2tBu$), 23.20 ($\underline{C}H_2CN$), 25.77 ($OSi(CH_3)_2\underline{C}(CH_3)_3$), 41.22 (C-3), 58.66 (C-2), 59.02 ($N\underline{C}H_2Ph$), 62.69 (C-5), 69.95 (C-4), 118.06 (CN), 127.17, 128.39, 128.55, 138.92 (C-Ar); Anal. calcd for $C_{19}H_{30}N_2OSi$: C, 69.04; H, 9.15; N, 8.47, found: C, 69.09; H, 9.08; N, 8.42; $[\alpha]_D^{20} = -41.0$ (*c* 0.63, $CHCl_3$).

Analytical data of **15**: Mp: 50–55°C; EI-MS $m/z = 330$ [M^+]); TLC: $R_f = 0.29$ (petroleum ether/EtOAc = 9:1); IR (film): ν 3026–2803, 2239, 1463, 1255, 1102, 837, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.03 (s, 3H, $OSi(C\underline{H}_3)_2tBu$), 0.05 (s, 3H, $OSi(C\underline{H}_3)_2tBu$), 0.08 (s, 9H, $OSi(CH_3)_2C(C\underline{H}_3)_3$), 1.64 (ddd, 1H, $J = 13.1$, 8.5, 4.7 Hz, H-4ax), 2.00 (brddd, 1H, $J = 13.1$, 5.0, 5.0 Hz, H-4eq), 2.23 (brdd, 1H, $J = 11.0$, 7.5 Hz, H-6a), 2.42 (brd, 1H, $J = 10.3$ Hz, H-2a), 2.72 (m, 2H, H-2b/H-6b), 3.03 (brddd, 1H, $J = 8.5$, 4.7, 5.0, H-3eq), 3.51 (d, 1H, $J = 13.7$ Hz, NCH_2Ph), 3.66 (d, 1H, $J = 13.7$ Hz, NCH_2Ph), 4.02 (dddd, 1H, $J = 8.5$, 7.5, 5.0, 4.7 Hz, H-5eq), 7.20–7.40 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 62.90 MHz): δ 18.00 ($OSi(\underline{C}H_3)_2tBu$), 25.74 (C-3), 35.83 (C-4), 53.86 (C-2), 60.08 (C-6), 61.92 ($N\underline{C}H_2Ph$), 65.16 (C-5), 121.26 (CN), 127.22, 128.33, 128.62, 137.61 (C-Ar); Anal. calcd for $C_{19}H_{30}N_2OSi$: C, 69.04; H, 9.15; N, 8.47, found: C, 69.09; H, 9.22; N, 8.40; $[\alpha]_D^{20} = +18.4$ (*c* 1.0, $CHCl_3$).

***ent*-12** and ***ent*-15** were prepared under the same reaction conditions as described for **12**, starting from ***ent*-9**.

4.11. (2*R*,4*R*)-[1-Benzyl-4-(*tert*-butyldimethylsilyloxy)-pyrrolidin-2-yl]acetonitrile 13

A mixture of **11** (279 mg, 0.87 mmol), NEt_3 (0.36 mL, 2.60 mmol), Ms_2O (378 mg, 2.17 mmol) and then a cold solution of LiCN (20 mL, 0.5 M in DMF) in $CHCl_3$ (15 mL) was reacted and worked up as described for **12** to give **13** (200.8 mg, 70%) as a colorless crystalline solid. Mp: 40°C; EI-MS $m/z=330$ [M^+], 290 (α-cleavage, [$M-CH_2CN]^+$); TLC: $R_f=0.07$ (petroleum ether/EtOAc = 95:5); IR (film): ν 3028–2801, 1471, 1360, 1255, 1099, 1031, 835, 776, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.01 (s, 3H, $OSi(C\underline{H}_3)_2C(CH_3)_3$), 0.03 (s, 3H, $OSi(C\underline{H}_3)_2C(CH_3)_3$), 0.87 (s, 9H, $OSi(CH_3)_2C(C\underline{H}_3)_3$), 1.80 (m, 1H, H-3a), 2.29 (ddd, 1H, $J=13.5$, 7.8, 5.7 Hz, H-3b), 2.54 (m, 2H, CH_2CN/CH_2CN), 2.60 (dd, 1H, $J=10.3$, 5.1 Hz, H-5a), 2.89 (brd, 1H, $J=10.3$ Hz, H-5b), 3.06 (m, 1H, H-2), 3.55 (d, 1H, $J=13.4$ Hz, NCH_2Ph), 3.93 (d, 1H, $J=13.4$ Hz, NCH_2Ph), 4.32 (m, 1H, H-4), 7.22–7.35 (m, 5H, Ar); Anal. calcd for $C_{19}H_{30}N_2OSi$ (330.55): C, 69.04; H, 9.15; N, 8.47, found: C, 69.07; H, 9.26; N, 8.51; $[\alpha]_D^{20}=+35.3$ (*c* 1.0, $CHCl_3$).

***ent*-13** was prepared under the same reaction conditions as described for **13**, starting from ***ent*-11**; $[\alpha]_D^{20}=-37.6$ (*c* 1.0, $CHCl_3$).

4.12. (2*S*,4*R*)-2-[1-Benzyl-4-(*tert*-butyldimethylsilyloxy)-pyrrolidin-2-yl]ethylamine 14

To a stirred solution of **12** (22.1 mg, 0.067 mmol) in Et_2O (5 mL) was added $LiAlH_4$ (0.17 mL, 1 M solution in Et_2O) at 0°C. After 2h, the reaction was quenched with an aqueous solution of saturated $NaHCO_3$, the mixture filtered through Celite and the filter cake extracted with MeOH. The filtrate was evaporated and the residue purified by flash chromatography (CH_2Cl_2/MeOH = 8:2+3 mL of NH_3-saturated MeOH/500 mL eluent) to leave pure **14** (14.40 mg, 64%) as a yellow oil; EI-MS $m/z=290$ (α-cleavage, $[M-CH_2CH_2NH_2]^+$); TLC: $R_f=0.28$ CH_2Cl_2/MeOH = 8:2+3 mL of NH_3-saturated MeOH/500 mL eluent); IR (film): ν 3292–2797, 1583, 1471, 1378, 1255, 1126, 835, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.01 (s, 6H, $OSi(C\underline{H}_3)_2C(CH_3)_3$), 0.86 (s, 9H, $OSi(CH_3)_2C(C\underline{H}_3)_3$), 1.56 (dddd, 1H, $J=$ 13.8, 7.9, 7.9, 6.0 Hz, H-3a), 1.81 (m, 3H, H-3b/H-6a/H-6b), 2.17 (dd, 1H, $J=9.9$, 5.5 Hz, H-5a), 2.35 (brs, 2H, $CH_2CH_2N\underline{H}_2$), 2.79 (m, 3H, $CH_2C\underline{H}_2N\underline{H}_2/CH_2C\underline{H}_2N\underline{H}_2$/H-2), 3.11 (dd, 1H, $J=9.9$, 6.2 Hz, H-5b), 3.28 (d, 1H, $J=12.8$ Hz, NCH_2Ph), 4.05 (d, 1H, $J=12.8$ Hz, NCH_2Ph), 4.29 (m, 1H, H-4), 7.20–7.36 (m, 5H, Ar); HR-EIMS: 171.1045752 (Anal. calcd for $C_{12}H_{13}N$: 171.10480), 304.21028 (Anal. calcd for $C_{18}H_{30}NOSi$: 304.20966); $[\alpha]_D^{20}=-68.0$ (*c* 1.0, $CHCl_3$).

4.13. (3*S*,5*R*)-(1-Benzyl-5-(*tert*-butyldimethylsilyloxy)-piperidin-3-yl)methylamine 16

A stirred solution of **15** (12.1 mg, 0.037 mmol) in Et_2O (5 mL) and $LiAlH_4$ (0.17 mL, 1 M solution in Et_2O) was reacted and worked up as described for **14** to give pure **16** (9.9 mg, 81%) as a yellow oil; EI-MS $m/z=304$ ($[M-CH_2NH_2]^+$); TLC: $R_f=0.32$ (CH_2Cl_2/MeOH 8:2+ 1.5 mL NH_3-saturated MeOH/1000 mL eluent); IR (NaCl): ν 3062–2799, 1575, 1471, 1387, 1359, 1304, 1253, 1091, 1037, 835, 775, 736, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.01 (s, 3H, $OSi(C\underline{H}_3)_2C(CH_3)_3$), 0.03 (s, 3H, $OSi(C\underline{H}_3)_2C(CH_3)_3$), 0.88 (s, 9H, $OSi(CH_3)_2C(C\underline{H}_3)_3$), 1.48 (m, 2H, H-4ax/H-4eq), 1.89 (m, 1H, H-3), 2.23 (dd, 1H, $J=10.8$, 6.2 Hz, H-2a), 2.31 (dd, 1H, $J=10.8$, 6.3 Hz, H-2b), 2.45 (m, 2H, CH_2NH_2/CH_2NH_2), 2.62 (dd, 1H, $J=12.6$, 6.2 Hz, H-6a), 2.72 (dd, 1H, $J=12.6$, 8.1 Hz, H-6b), 3.38 (d, 1H, $J=13.5$ Hz, NCH_2Ph), 3.64 (d, 1H, $J=13.5$ Hz, NCH_2Ph), 3.91 (m, 1H, H-5), 7.18–7.37 (m, 5H, Ar); HR-EIMS: 304.20901 (Anal. calcd for $C_{18}H_{30}NOSi$: 304.20966), 172.11297 (Anal. calcd for $C_{12}H_{14}N$: 172.11263); $[\alpha]_D^{20}=+42.2$ (*c* 0.32, $CHCl_3$).

4.14. (3*R*,5*R*)-1-Benzyl-5-hydroxypiperidine-3-carboxylic acid hydrochloride 18

To **15** (10.3 mg, 0.03 mmol) was added conc. HCl (15 mL) and the mixture refluxed for 2 h. After cooling to rt, the mixture was evaporated to leave **18** (8.4 mg, 99%) as a white solid. Mp: 210–220°C; EI-MS $m/z=$ 235 ([M-HCl]$^+$); IR (film): ν 3363, 2923, 2360, 1731, 1650, 1457, 1434, 1037, 898 cm^{-1}; ^1H NMR (D_2O, 360 MHz): δ 1.76 (ddd, 1H, $J=14.2$, 12.9, 1.8 Hz, H-4a), 2.20 (brd, 1H, $J=14.2$ Hz, H-4b), 3.03–3.33 (m, 4H, H-6a, H-6b, H-2a, H-2b), 3.71 (brd, 1H, $J=11.7$ Hz, H-3), 4.30 (d, 1H, $J=13.2$ Hz, NCH_2Ph), 4.40 (d, 1H, $J=13.2$ Hz, NCH_2Ph), 4.70 (m, 1H, H-5/D_2O), 7.44–7.54 (m, 5H, Ar); HR-EIMS: 235.12121 (Anal. calcd for $C_{13}H_{17}NO_3$: 235.12085), 190.08714 (Anal. calcd for $C_{11}H_{12}NO_2$: 190.08681), 144.06660 (Anal. calcd for $C_6H_{10}NO_3$: 144.06607); $[\alpha]_D^{20}=-0.2$ (*c* 2.68, MeOH).

4.15. (3*R*,5*S*)-1-Benzyl-5-hydroxymethylpyrrolidin-3-ol 19

Compound ***ent*-19** has already been described in the literature[2,12]. According to literature[2,12] preparation of **19** was performed in a slightly modified way as follows. To a stirred solution of **6** (69.7 mg, 0.28 mmol) in THF (10 mL) was added $LiAlH_4$ (0.54 mL, 1 M solution in THF) at 0°C. After 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was filtered through Celite and the filter cake extracted with CH_2Cl_2 (3×10 mL). The filtrate was evaporated to leave pure **19** (57.2 mg, 98%) as a colorless oil; EI-MS $m/z=207$ [M^+]; TLC: $R_f=0.18$ (CH_2Cl_2/MeOH = 9:1); IR (film): ν 3360, 1495, 1454, 1097, 1029, 749, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 1.85 (ddd, 1H, $J=13.1$, 8.3, 4.2 Hz, H-4a), 2.17 (ddd, 1H, $J=13.1$, 7.3, 7.5 Hz, H-4b), 2.40 (dd, 1H, $J=10.1$, 5.0 Hz, H-2a), 3.07 (m, 1H, H-5), 3.27 (dd, 1H, $J=10.1$, 5.5 Hz, H-2b), 3.41 (dd, 1H, $J=11.0$, 1.7 Hz, CH_2OH), 3.49 (d, 1H, $J=$ 13.0 Hz, NCH_2Ph), 3.66 (dd, 1H, $J=11.0$, 3.4 Hz, CH_2OH), 4.00 (d, 1H, $J=13.0$ Hz, NCH_2Ph), 4.32 (m, 1H, H-3), 7.20–7.38 (m, 5H, Ar); $[\alpha]_D^{20}=-58.4$ (*c* 1.0, $CHCl_3$), {lit.: $[\alpha]_D^{20}=-79.8$, (*c* 1.12, MeOH)}.

***ent*-19** was prepared under the same reaction conditions, starting from ***ent*-6**; $[\alpha]_D^{20}=+63.4$ (*c* 0.6, $CHCl_3$).

4.16. (3*R*,5*R*)-1-Benzyl-5-hydroxymethylpyrrolidin-3-ol 20

A mixture of **7** (44.6 mg, 0.18 mmol) and $LiAlH_4$ (0.32 mL, 1 M solution in THF) in THF (8 mL) was reacted and worked up (eluent for flash chromatography: CH_2Cl_2/MeOH = 95:5) as described for **19** to leave pure **20** (36.5 mg, 98%) as opaque crystals. Mp: 41–42°C; EI-MS $m/z = 207$ [M^+]; TLC: $R_f = 0.10$ (CH_2Cl_2/MeOH = 95:5); IR (film): ν 3363, 3025–2796, 1452, 1338, 1132, 1025, 746, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 1.79 (brd, 1H, $J = 14.2$ Hz, H-4a), 2.35 (ddd, 1H, $J = 14.2$, 10.3, 6.0 Hz, H-4b), 2.45 (dd, 1H, $J = 10.1$, 3.7 Hz, H-2a), 2.86 (m, 1H, H-5), 3.00 (dd, 1H, $J = 10.1$, 2.0 Hz, H-2b), 3.39 (dd, 1H, $J = 11.1$, 1.4 Hz, CH_2OH), 3.49 (d, 1H, $J = 13.3$ Hz, NCH_2Ph), 3.58 (dd, 1H, $J = 11.1$, 3.0 Hz, CH_2OH), 3.93 (d, 1H, $J = 13.3$ Hz, NCH_2Ph), 4.19 (m, 1H, H-3), 7.22–7.37 (m, 5H, Ar); Anal. calcd for $C_{12}H_{17}NO_2$ (207.27): C, 69.54; H, 8.27; N, 6.76, found: C, 69.24; H, 8.41; N, 6.65; $[\alpha]_D^{20} = +35.8$ (*c* 1.0, $CHCl_3$).

***ent*-20** was prepared under the same reaction conditions as described for **20**, starting from ***ent*-7**; $[\alpha]_D^{20} = -37.2$ (*c* 1.2, $CHCl_3$).

4.17. (3*R*,5*S*)-1-Benzyl-5-chloromethylpyrrolidin-3-ol hydrochloride 21

A mixture of **19** (316 mg, 1.53 mmol) and $SOCl_2$ (0.16 mL, 2.3 mmol) in $CHCl_3$ (15 mL) was reacted and worked up as described for **22** to leave pure **21** (292 mg, 85%) as an opaque, creamy mass; EI-MS $m/z = 225$ [M^+]; TLC: $R_f = 0.15$ (petroleum ether/EtOAc = 8:2); IR (film): ν 3316, 2935, 2584, 1454, 1214, 1103, 995, 748, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 2.10 (m, 1H, H-4a), 2.52 (m, 1H, H-4b), 3.39 (brd, 1H, $J = 11.4$ Hz, H-2a), 3.80 (m, 3H, H-2b/H-5/NCH_2Ph), 4.12 (m, 1H, CH_2Cl), 4.45 (brdd, 1H, $J = 13.0$, 5.9 Hz, CH_2Cl), 4.65 (m, 2H, NCH_2Ph/H-3), 7.22–7.75 (m, 5H, Ar); HR-EIMS: 225.09184 (Anal. calcd for $C_{12}H_{16}NOCl$: 225.09204), 134.03798 (Anal. calcd for C_5H_9NOCl: 134.03726); $[\alpha]_D^{20} = +2.3$ (*c* 1.0, $CHCl_3$).

***ent*-21** was prepared under the same reaction conditions as described for **21**, starting from ***ent*-19**; $[\alpha]_D^{20} = -2.2$ (*c* 0.8, $CHCl_3$).

4.18. (3*R*,5*R*)-1-Benzyl-5-chloromethylpyrrolidin-3-ol hydrochloride 22

To a solution of **20** (341 mg, 1.64 mmol) in $CHCl_3$ (20 mL) was added $SOCl_2$ (0.18 mL, 2.46 mmol) after which the mixture was refluxed for 3.5 h. After cooling to rt, the mixture was extracted with acetone/H_2O (1:1) and the acetone/H_2O-layer then evaporated to leave pure **22** (334.3 mg, 80%) as an opaque, creamy mass; EI-MS $m/z = 225$ [M^+]; TLC: $R_f = 0.07$ (petroleum ether/EtOAc = 8:2); IR (film): ν 3309, 3066–2611, 1454, 1214, 1052, 752, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 2.07 (brdd, 1H, $J = 14.6$, 4.6 Hz, H-4a), 2.34 (ddd, 1H, $J = 14.6$, 9.9, 5.3 Hz, H-4b), 3.02 (brd, 1H, $J = 10.6$ Hz, H-2a), 3.69 (m, 2H, H-2b/H-5), 3.96 (dd, 1H, $J = 13.1$, 3.2 Hz, CH_2Cl), 4.17 (dd, 1H, $J = 13.1$, 7.5 Hz, CH_2Cl), 4.29 (d, 1H, $J = 13.1$ Hz, NCH_2Ph), 4.49 (m, 1H, H-3), 4.61 (d, 1H, $J = 13.1$ Hz, NCH_2Ph), 5.00 (brs, 1H, -OH), 7.23–7.64 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 90.56 MHz): δ 35.70 (C-3), 58.20 (C-2), 58.33 (NCH_2Ph), 61.25 (C-5), 62.13 (CH_2Cl), 68.01 (C-2), 68.25 (C-4), 128.66, 129.27, 131.65, 130.34 (C-Ar); HR-EIMS: 225.09184 (Anal. calcd for $C_{12}H_{16}NOCl$: 225.09204), 176.10749 (Anal. calcd for $C_{11}H_{14}NO$: 176.10754), 134.03759 (Anal. calcd for C_5H_9NOCl: 134.03726); $[\alpha]_D^{20} = +8.8$ (*c* 0.1, $CHCl_3$).

***ent*-22** was prepared under the same reaction conditions as described for **22**, starting from ***ent*-20**; $[\alpha]_D^{20} = -8.3$ (*c* 0.1, $CHCl_3$).

4.19. (2*S*,4*R*)-(1-Benzyl-4-hydroxypyrrolidin-2-yl)-acetonitrile 23 and (3*R*,5*R*)-1-benzyl-5-hydroxypiperidine-3-carbonitrile 27

To a solution of **21** (130 mg, 0.5 mmol) in 80% EtOH (25 mL) was added NaCN (460 mg, 9.4 mmol) and the mixture allowed to reflux for 24 h. After cooling to rt, an aqueous saturated solution of $NaHCO_3$ was added and the mixture extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc = 85:15) to give a diastereomeric mixture of **23** and **24** and the piperidine **27** in an overall yield of 60.8 mg (57%). **23** and **24** were isolated as colorless oils and **27** isolated as a white, crystalline solid. Mp: 104–105°C.

Analytical data of **23**: colorless oil; EI-MS $m/z = 216$ [M^+], 176 (α-cleavage, [$M-CH_2CN]^+$); TLC: $R_f = 0.10$ (petrolum ether/EtOAc = 6:4); IR (film): ν 3421, 3085–2807, 2248, 1450, 1353, 1130, 1091, 744, 701 cm^{-1}; 1H NMR ($CDCl_3$, 360 MHz): δ 2.05 (m, 2H, H-3a/H-3b), 2.38 (dd, 1H, $J = 10.6$, 4.6 Hz, H-5a), 2.43 (dd, 1H, $J = 16.8$, 6.2 Hz, CH_2CN), 2.49 (dd, 1H, $J = 16.8$, 3.8 Hz, CH_2CN), 3.18 (m, 1H, H-2), 3.34 (dd, 1H, $J = 10.6$, 5.5 Hz, H-5b), 3.55 (d, 1H, $J = 13.2$ Hz, NCH_2Ph), 3.96 (d, 1H, $J = 13.2$ Hz, NCH_2Ph), 4.46 (m, 1H, H-4), 7.21–7.40 (m, 5H, Ar); Anal. calcd for $C_{13}H_{16}N_2O$ (216.29): C, 72.19; H, 7.46; N, 12.95, found: C, 72.06; H, 7.42; N, 12.82; $[\alpha]_D^{20} = -67.1$ (*c* 1.0, $CHCl_3$).

***ent*-23** was prepared under the same reaction conditions as described for **23**, starting from ***ent*-21**; $[\alpha]_D^{20} = +62.7$ (*c* 0.75, $CHCl_3$).

Analytical data of **27**: white crystalline solid; Mp: 104–105°C; EI-MS $m/z = 216$ [M^+]; TLC: $R_f = 0.14$ (petroleum ether/EtOAc = 6:4); IR (film): ν 3432, 2919, 2807, 2240, 1600, 1153, 1045, 941, 748, 698 cm^{-1}; 1H NMR ($CDCl_3$, 360 MHz, at 330 K): δ 1.72 (ddd, 1H, $J = 13.3$, 10.3, 3.0 Hz, H-4ax), 1.92 (ddd, 1H, $J = 13.3$, 4.8, 4.3 Hz, H-4eq), 2.35 (m, 2H, H-2a/H-6a), 2.58 (dd, 1H, $J = 11.7$, 5.0 Hz, H-6b), 2.80 (dd, 1H, $J = 10.6$, 4.5 Hz, H-2b), 2.96 (dddd, 1H, $J = 9.5$, 10.3, 4.5, 4.8 Hz, H-3ax), 3.50 (s, 2H, NCH_2Ph/NCH_2Ph), 3.91 (m, 1H, H-5eq), 7.16–7.28 (m, 5H, Ar); Anal. calcd for $C_{13}H_{16}N_2O$ (216.29): C, 72.19; H, 7.46; N, 12.95, found: C, 72.26; H, 7.57; N, 12.83; $[\alpha]_D^{20} = -7.0$ (*c* 1.0, $CHCl_3$).

***ent*-27** was prepared under the same reaction conditions as described for **27**, starting from ***ent*-21**; $[\alpha]_D^{20} = +11.5$ (*c* 0.21, $CHCl_3$).

4.20. (2*R*,4*R*)-(1-Benzyl-4-hydroxypyrrolidin-2-yl)-acetonitrile 24 and (3*S*,5*R*)-1-benzyl-5-hydroxy-piperidine-3-carbonitrile 28

A solution of **22** (224 mg, 0.85 mmol) and NaCN (400.0 mg, 8.16 mmol) in 80% EtOH (25 mL) were reacted and worked up (petroleum ether/EtOAc = 1:1) as described in section 4.20. to give **24**, **23** and **28** (overall yield: 139 mg, 76%).

Analytical data of **24**: colorless oil; EI-MS $m/z = 216$ [M^+]; TLC: $R_f = 0.1$ (petroleum ether/EtOAc = 1:1); IR (film): ν 3428, 3062–2807, 2248, 1492, 1450, 1349, 1130, 1076, 748, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 1.79 (brdd, 1H, $J = 14.6$, 5.3 Hz, H-3a), 2.48 (m, 4H, H-3b/H-5a/CH_2CN/CH_2CN), 2.86 (m, 1H, H-2), 2.99 (dd, 1H, $J = 10.5$, 1.2 Hz, H-5b), 3.48 (d, 1H, $J = 13.0$ Hz, NCH_2Ph), 3.93 (d, 1H, $J = 13.0$ Hz, NCH_2Ph), 4.23 (m, 1H, H-4), 7.25–7.36 (m, 5H, Ar); HR-EIMS: 216.12651 (Anal. calcd for $C_{13}H_{16}N_2O$: 216.12627), 176.10749 (Anal. calcd for $C_{11}H_{14}NO$: 176.10754); $[\alpha]_D^{20} = +40.3$ (*c* 0.3, $CHCl_3$).

Analytical data of **28**: colorless oil; EI-MS $m/z = 216$ [M^+]; TLC: $R_f = 0.15$ (petroleum ether/EtOAc = 1:1); IR (film): ν 3390, 3062–2807, 2240, 1454, 1361, 1153, 1068, 941, 748, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 1.78 (m, 1H, H-4a), 2.06 (brd, 1H, $J = 13.0$ Hz, H-2a), 2.39 (m, 2H, H-4b/H-6a), 2.71 (brd, 1H, $J = 9.3$ Hz, H-6b), 2.93 (brd, 1H, $J = 13.0$ Hz, H-2b), 3.05 (m, 1H, H-3), 3.58 (s, 2H, NCH_2Ph/NCH_2Ph), 4.00 (m, 1H, H-5), 7.25–7.36 (m, 5H, Ar); HR-EIMS: 216.12629 (Anal. calcd for $C_{13}H_{16}N_2O$: 216.12627), 171.09202 (Anal. calcd for $C_{11}H_{11}N_2$: 171.09222), 125.07116 (Anal. calcd for $C_6H_9N_2O$: 125.07149); $[\alpha]_D^{20} = +17.3$ (*c* 0.13, $CHCl_3$).

***ent*-24** $[\alpha]_D^{20} = -42.1$ (*c* 1.0, $CHCl_3$) and ***ent*-28** $[\alpha]_D^{20} = -18.5$ (*c* 0.3, $CHCl_3$) were prepared under the same reaction conditions as described for **24** and **28**, starting from ***ent*-22**.

4.21. (3*R*,5*R*)-5-(2-Aminoethyl)-1-benzylpyrrolidin-3-ol 25

A mixture of **23** (24.7 mg, 0.11 mmol) and $LiAlH_4$ (0.23 mL, 1 M solution in THF) in THF (5 mL) were reacted and worked up as described for **19** to leave crude **25**. Crude **25** was used for the next reaction step without further purification.

***ent*-25** was prepared under the same reaction conditions as described for **25**, starting from ***ent*-23**.

4.22. (3*R*,5*S*)-5-(2-Aminoethyl)-1-benzylpyrrolidin-3-ol 26

A mixture of **24** (13.7 mg, 0.06 mmol) and $LiAlH_4$ (0.13 mL, 1 M solution in THF) in THF (10 mL) were reacted and worked up as described for **19** to leave crude **26**. Crude **26** was used for the next reaction step without further purification.

***ent*-26** was prepared under the same reaction conditions as described for **26**, starting from ***ent*-24**.

4.23. Ethyl (2*S*,4*S*)-1-benzyl-4-methylprolinate 30 and (3*R*,5*S*)-[1-benzyl-5-(1-hydroxy-1-methylethyl)-pyrrolidin-3-yl]tosylate 32

A suspension of Cu(I)I (3728 mg, 1.96 mmol) in Et_2O (10 mL) and a solution of MeLi (2.3 mL, 1.6 M in Et_2O) were reacted as described for **39**. Compound **29** (107 mg, 0.27 mmol) in Et_2O was then added. The mixture was further reacted and worked up to give **30** (7.5 mg, 11%) as a colorless oil as well as **32**, a white solid, as the main product (31.7 mg, 55%).

Analytical data of **30**: EI-MS $m/z = 247.3$ [M^+]; 174 (α-cleavage, [$M-CO_2C_2H_5$]$^+$); TLC: $R_f = 0.42$ (petroleum ether/EtOAc = 8:2); IR (film): ν 3033–2800, 1729, 1454, 1375, 1183, 1029, 745, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 1.05 (d, 3H, $J = 6.5$ Hz, CH_3), 1.25 (t, 3H, $J = 7.0$ Hz, $CO_2CH_2CH_3$), 1.58 (ddd, 1H, $J = 12.2$, 7.5, 7.2 Hz, H-3a), 2.27 (m, 2H, H-4/H-3b), 2.65 (m, 2H, H-5a/H-5b), 3.36 (dd, 1H, $J = 7.9$, 7.5 Hz, H-2), 3.55 (d, 1H, $J = 13.2$ Hz, NCH_2Ph), 3.92 (d, 1H, $J = 13.2$ Hz, NCH_2Ph), 4.14 (m, 2H, $CO_2CH_2CH_3$), 7.20–7.37 (m, 5H, Ar); HR-EIMS: 174.12835 (Anal. calcd for $C_{12}H_{16}N$: 174.12828); $[\alpha]_D^{20} = -43.2$ (*c* 0.04, $CHCl_3$).

4.24. Ethyl (2*S*,4*S*)-1-benzyl-4-butylprolinate 31

A suspension of Cu(I)I (90.2 mg, 0.48 mmol) in Et_2O (10 mL) and *n*-BuLi (0.53 mL, 1.6 M in Et_2O) was reacted as described for **40**. A solution of **29** (108 mg, 0.27 mol) in Et_2O was then added and the reaction and work-up performed to give **31** (18.7 mg, 24%) as a colorless oil. EI-MS $m/z = 216$ (α-cleavage, [$M-CO_2C_2H_5$]$^+$); TLC: $R_f = 0.7$ (petroleum ether/EtOAc = 1:1); IR (film): ν 2956–2857, 1730, 1454, 1375, 1180, 1028, 739, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.88 (m, 6H, $CO_2CH_2CH_3$/$CH_2CH_2CH_2CH_3$), 1.30 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.60 (m, 1H, H-3a), 2.09 (ddd, 1H, $J = 14.5$, 7.2, 7.5 Hz, H-3b), 2.29 (m, 1H, H-4), 2.62 (dd, 1H, $J = 8.6$, 8.9 Hz, H-5a), 2.72 (dd, 1H, $J = 8.9$, 6.0 Hz, H-5b), 3.36 (dd, 1H, $J = 7.8$, 7.5 Hz, H-2), 3.55 (d, 1H, $J = 13.0$ Hz, NCH_2Ph), 3.91 (d, 1H, $J = 13.0$ Hz, NCH_2Ph), 4.13 (q, 2H, $J = 6.7$ Hz, $CO_2CH_2CH_3$), 7.18–7.40 (m, 5H, Ar).

A second experiment was performed using 11 equivalents of Bu_2CuLi and prolonged reaction conditions (3.5 h) to give **31** in an overall yield of 45%.

4.25. (3*R*,5*S*)-[1-Benzyl-5-(1-hydroxy-1-methylethyl)-pyrrolidin-3-yl]tosylate 32

To a solution of **29** (68.6 mg, 0.17 mmol) in THF (10 mL) was added Li_2CuCl_4 (0.05 mL, 0.1 M in THF) at

0°C after which the mixture was stirred for 15 min. A solution of MeMgBr (0.07 mL, 3 M in Et_2O) was then added and the mixture stirred for another 3 h. Then the mixture was extracted with Et_2O and the organic layer dried over $MgSO_4$ and evaporated. The resulting residue was purified by flash chromatography (petroleum ether/EtOAc, 9:1) to leave **32** (56.6 mg, 86%); Mp: 51–52°C; EI-MS $m/z=374$ ($[M-CH_3]^+$); TLC: $R_f=0.07$ (petroleum ether/EtOAc=8:2); IR (film): ν 3454, 3028–2862, 1453, 1363, 1176, 897, 723 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 1.09 (s, 3H, $C(C\underline{H}_3)_2$), 1.27 (s, 3H, $C(C\underline{H}_3)_2$), 1.99 (ddd, 1H, $J=$ 14.1, 8.8, 4.8 Hz, H-4a), 2.16 (m, 1H, H-4b), 2.44 (s, 3H, $OSO_2C_6H_4C\underline{H}_3$), 2.83 (brd, 1H, $J=13.4$ Hz, H-2a), 2.93 (dd, 1H, $J=13.4$, 3.4 Hz, H-2b), 3.12 (dd, 1H, $J=8.8$, 7.5 Hz, H-5), 3.84 (d, 1H, $J=14.1$ Hz, NCH_2Ph), 4.06 (d, 1H, $J=14.1$ Hz, NCH_2Ph), 4.93 (m, 1H, H-3), 7.22–7.37 (m, 7H, Ar/$OSO_2C_6\underline{H}_4CH_3$), 7.79 (m, 2H, $OSO_2C_6\underline{H}_4CH_3$); Anal. calcd for $C_{21}H_{27}NO_4S$ (389.52): C, 64.76; H, 6.99; N, 3.60; S, 8.23, found: C, 64.77; H, 6.95; N, 3.66; S, 8.30; $[\alpha]_D^{20}=-26.1$ (c 0.23, $CHCl_3$).

4.26. (2*S*,4*R*)-[1-Benzyl-5-(1-butyl-1-hydroxypentyl)-pyrrolidin-3-yl]tosylate 33

To a suspension of CuCN (29.0 mg, 0.32 mmol) in Et_2O (10 mL) was added a solution of BuLi (0.36 mL, 1.6 M in hexane) at −40°C. The mixture was allowed to warm up to 0°C and then stirred for 15 min. Afterwards the mixture was cooled down to −40°C again whereupon **29** (73.6 mg, 0.18 mmol) in Et_2O was added and stirring continued at −40°C for another 3 h. An aqueous saturated solution of NH_4Cl was added and the mixture extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc=95:5) to give **33** (36.1 mg, 42%) as a white crystalline solid. Mp: 69–72°C; TLC: $R_f=0.60$ (petroleum ether/EtOAc, 1:1); IR (KBr): ν 3029–2870, 1713, 1598, 1494, 1454, 1365, 1176, 1097, 891, 815, 723, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.89 (m, 6H, $CH_2CH_2CH_2C\underline{H}_3$/$CH_2CH_2CH_2C\underline{H}_3$), 1.17–1.49 (m, 13H, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$/$C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$/H-3a), 2.06 (m, 1H, H-3b), 2.40 (dd, 1H, $J=12.96$, 7.4 Hz, H-5a), 2.44 (s, 3H, $OSO_2C_6H_4C\underline{H}_3$), 3.24 (m, 1H, H-5b), 3.47 (dd, 1H, $J=8.4$, 4.6 Hz, H-2), 3.86 (d, 1H, $J=13.7$ Hz, NCH_2Ph), 3.95 (d, 1H, $J=13.7$ Hz, NCH_2Ph), 4.93 (m, 1H, H-4), 7.24–7.34 (m, 7H, Ar/$OSO_2C_6\underline{H}_4CH_3$), 7.8 (m, 2H, $OSO_2C_6\underline{H}_4CH_3$); Anal. calcd for $C_{27}H_{39}NO_4S$ (473.68): C, 68.46; H, 8.30; N, 2.96; S, 6.77, found: C, 68.52; H, 8.23; N, 3.02; S, 6.66; $[\alpha]_D^{20}=-28.8$ (c 0.8, $CHCl_3$).

4.27. Ethyl (2*S*)-2-benzylaminopent-4-enoate 34

Zinc drops (four pieces) were dipped into conc. HCl, washed with EtOH/acetone (1:1) and then placed into a flask, containing DMF (15 mL). A solution of **36** (51.4 mg, 0.14 mmol) in DMF was added and the mixture was stirred at rt for 1.5 h. Then, $Pd_2(dba)_3$ (4.12 mg, 0.0043 mmol), P(o-Tol)$_3$ (5.61 mg, 0.018 mmol) and C_6H_5I (20.3 μL, 0.18 mmol) were added. After stirring for another 24 h, the mixture was diluted with EtOAc (15 mL) and washed with brine. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc=9:1) to give **34** (31.0 mg, 94%) as a colorless oil; EI-MS $m/z=233$ [M^+]; TLC: $R_f=0.12$ (petroleum ether/EtOAc=9:1); IR (film): ν 3066–2935, 1731, 1454, 1184, 1025, 740, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 1.28 (t, 3H, $J=7.0$ Hz, $CO_2CH_2C\underline{H}_3$), 2.43 (m, 2H, H-3a/H-3b), 3.35 (dd, 1H, $J=6.5$, 6.5 Hz, H-2), 3.67 (d, 1H, $J=13.0$ Hz, NCH_2Ph), 3.83 (d, 1H, $J=$ 13.0 Hz, NCH_2Ph), 4.19 (m, 2H, $CO_2C\underline{H}_2CH_3$), 5.10 (m, 2H, H-5a/H-5b), 5.77 (m, 1H, H-4), 7.22–7.35 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 90.56 MHz): δ 14.35 ($CO_2CH_2\underline{C}H_3$), 37.71 (C-3), 60.24 (C-2), 60.62 ($CO_2\underline{C}H_2CH_3$), 117.92 (CH_2-$\underline{C}H$=CH_2), 51.95 ($N\underline{C}H_2Ph$), 127.05, 128.25, 128.36, 133.67 (C-Ar), 139.75 (-CH=$\underline{C}H_2$); Anal. calcd for $C_{14}H_{19}NO_2$ (233.31): C, 72.07; H, 8.21; N, 6.00, found: C, 71.87; H, 8.39; N, 5.90; $[\alpha]_D^{20}=-18.0$ (c 0.28, $CHCl_3$).

4.28. Ethyl (2*S*,4*R*,*S*)-1-benzyl-4-iodoprolinate 35,36

To a solution of **29** (2.09 g, 5.16 mmol) in acetone (50 mL) was added NaI (15.3 mg, 130 mmol) after which the mixture was refluxed for 48 h. After cooling to rt, the mixture was evaporated and the resulting residue extracted in Et_2O. To improve the yield of compounds **35** and **36**, the extracted residue was redissolved in acetone, evaporated and the resulting residue washed again with Et_2O (three times). The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc=97:3) to give a diastereomeric mixture of **35** and **36** (1.807 g, 97%) as a brown liquid.

Analytical data of **35**: EI-MS $m/z=358$ [M^+]; TLC: $R_f=0.21$ (petroleum ether/EtOAc=9:1); IR (film): ν 3085–2803, 1735, 1450, 1373, 1272, 1187, 1029, 744, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 1.24 (t, 3H, $J=7.0$ Hz, $CO_2CH_2C\underline{H}_3$), 2.53 (ddd, 1H, $J=13.8$, 8.8, 7.1 Hz, H-3a), 2.62 (ddd, 1H, $J=13.8$, 7.9, 6.0 Hz, H-3b), 2.93 (dd, 1H, $J=9.9$, 7.5 Hz, H-5a), 3.54 (m, 2H, H-5b/H-2), 3.69 (d, 1H, $J=13.0$ Hz, NCH_2Ph), 4.03 (d, 1H, $J=13.0$ Hz, NCH_2Ph), 4.13 (m, 2H, $CO_2C\underline{H}_2CH_3$), 4.28 (m, 1H, H-4), 7.22–7.37 (m, 5H, Ar); Anal. calcd for $C_{14}H_{18}INO_2$ (359.21): C, 46.81; H, 5.05; N, 3.90, found: C, 46.94; H, 5.03; N, 3.82; $[\alpha]_D^{20}=$ −62.1 (c 1.0, $CHCl_3$).

Analytical data of **36**: EI-MS $m/z=358$ [M^+], 360 [M^+]; TLC: $R_f=0.27$ (petroleum ether/EtOAc=9:1); IR (film): ν 3062–2803, 1735, 1450, 1187, 1029, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 1.28 (t, 3H, $J=7.0$ Hz, $CO_2CH_2C\underline{H}_3$), 2.50 (ddd, 1H, $J=14.0$, 8.1, 6.7 Hz, H-3a), 2.83 (ddd, 1H, $J=14.0$, 6.9, 6.7 Hz, H-3b), 3.05 (dd, 1H, $J=10.8$, 6.5 Hz, H-5a), 3.35 (m, 1H, $J=10.8$, 5.8 Hz, H-5b), 3.52 (dd, 1H, $J=8.1$, 6.7 Hz, H-2), 3.74 (d, 1H, $J=13.4$ Hz, NCH_2Ph), 4.04 (d, 1H, $J=13.4$ Hz, NCH_2Ph), 4.20 (m, 3H, $CO_2C\underline{H}_2CH_3$/H-4), 7.22–7.44

(m, 5H, Ar); Anal. calcd for $C_{14}H_{18}INO_2$ (359.21): C, 46.81; H, 5.05; N, 3.90, found: C, 46.92; H, 4.96; N, 3.82; $[\alpha]_D^{20} = -20.9$ (*c* 1.0, $CHCl_3$).

***ent*-35** and ***ent*-36** were prepared under the same reaction conditions.

4.29. Ethyl (2*S*,4*R*,*S*)-1-benzyl-4-phenylprolinate 37

Zinc drops (four pieces) were prepared as described for **34**. A diastereomeric mixture of **35** and **36** (87.2 mg, 0.24 mmol) in DMF, was then added and the mixture stirred at rt for 4 h. $Pd_2(dba)_3$ (6.99 mg, 0.0072 mmol), P(*o*-Tol)$_3$ (9.47 mg, 0.03 mmol) and C_6H_5I (34.26 μL, 0.31 mmol) were added and the mixture reacted and worked up (petroleum ether/EtOAc = 9:1) to give **34** and a diastereomeric mixture of **37** (41.2 mg, 55%); EI-MS $m/z = 309$ [M^+]; TLC: $R_f = 0.06$ (petroleum ether/EtOAc = 9:1); IR (film): *v* 3060–2814, 1730, 1453, 1182, 1027, 741, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ *1.25 (t, 3H, $J = 7.0$ Hz, $CO_2CH_2C\underline{H}_3$), 1.26 (t, 3H, $J = 7.0$ Hz, $CO_2CH_2C\underline{H}_3$), 1.76 (m, 2H, 2×H-3), 1.92 (m, 3H, 2×H-3/H-4), 2.13 (m, 1H, H-4), 2.40 (dd, 1H, $J = 8.6$, 8.6 Hz, H-2 or H-5), 2.58 (m, 2H, H-5 or H-2), 3.03 (m, 1H, H-2 or H-5), 3.23 (dd, 1H, $J = 8.7$, 6.3 Hz, H-2 or H-5), 3.41 (dd, 1H, $J = 6.5$, 6.5 Hz, H-5 or H-2), 3.55 (d, 1H, $J = 13.0$ Hz, NCH_2Ph), 3.69 (d, 1H, $J = 13.4$ Hz, NCH_2Ph), 3.86 (d, 1H, $J = 13.0$ Hz, NCH_2Ph), 3.92 (d, 1H, $J = 13.4$ Hz, NCH_2Ph), 4.13 (m, 2H, $CO_2C\underline{H}_2CH_3$), 4.19 (m, 2H, $CO_2C\underline{H}_2CH_3$), 7.15–7.40 (m, 10H, Ar). Anal. calcd for $C_{20}H_{23}NO_2$ (309.41): C, 77.64; H, 7.49; N, 4.53, found: C, 77.62; H, 7.57; N, 4.48.

*Signals were not exactly related to each diastereomer.

4.30. Ethyl (2*R*,4*S*)-1-benzyl-4-methylprolinate 39

To a suspension of Cu(I)I (330 mg, 1.74 mmol) in Et_2O (10 mL) was added a solution of MeLi (2.02 mL, 1.6 M in Et_2O) at −20°C. The mixture was allowed to warm up to 0°C and stirring continued for 30 min. A solution of **38** (107 mg, 0.27 mmol) in Et_2O was then added to the mixture. After another 1.5 h, an aqueous saturated solution of Na_2CO_3 was added and the mixture extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc = 9:1) to give **39** (46.1 mg, 70%) as a colorless oil; EI-MS $m/z = 247$ [M^+]; TLC: $R_f = 0.38$ (petroleum ether/EtOAc = 8:2); IR (film): *v* 3027–2792, 1745, 1454, 1375, 1271, 1182, 1029, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.98 (d, 3H, $J = 6.5$ Hz, CH_3), 1.24 (t, 3H, $J = 7.0$ Hz, $CO_2CH_2C\underline{H}_3$), 1.69 (ddd, 1H, $J = 12.7$, 9.6, 7.9 Hz, H-3a), 1.99 (dd, 1H, $J = 8.9$, 8.9 Hz, H-5a), 2.14 (ddd, 1H, $J = 12.7$, 8.9, 5.9 Hz, H-3b), 2.34 (m, 1H, H-4), 3.13 (dd, 1H, $J = 8.9$, 6.9 Hz, H-5b), 3.29 (dd, 1H, $J = 9.6$, 5.9 Hz, H-2), 3.52 (d, 1H, $J = 12.7$ Hz, NCH_2Ph), 3.92 (d, 1H, $J = 12.7$ Hz, NCH_2Ph), 4.11 (m, 2H, $CO_2C\underline{H}_2CH_3$), 7.20–7.36 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 62.90 MHz): δ 1424 ($CO_2CH_2\underline{C}H_3$), 18.83 ($\underline{C}H_3$), 31.35 (C-4), 37.72 (C-3), 59.14 ($N\underline{C}H_2Ph$), 60.46 ($CO_2\underline{C}H_2CH_3$), 61.54 (C-5), 65.33 (C-2), 127.02, 128.13, 129.20, 138.47 (C-Ar); Anal. calcd for $C_{15}H_{21}NO_2$ (247.34): C, 72.84; H, 8.56; N, 5.66, found: C, 72.63; H, 8.54; N, 5.48; $[\alpha]_D^{20} = +48.7$ (*c* 1.0, $CHCl_3$).

***ent*-39** $[\alpha]_D^{20} = -52.5$ (*c* 1.0, $CHCl_3$) was prepared under the same reaction conditions as those described for **39**, starting from ***ent*-38**.

4.31. Ethyl (2*R*,4*S*)-1-benzyl-4-butylprolinate 40

To a suspension of Cu(I)I (1.7 g, 9.16 mmol) in Et_2O (250 mL) was added a solution of n-BuLi (10.1 mL, 1.6 M in hexane) at −50°C. The mixture was allowed to warm up to −20°C. After 30 min, **38** (2.06 g, 5.09 mmol), dissolved in Et_2O, was added and stirring continued for another 2 h at −20°C. An aqueous saturated solution of Na_2CO_3 was added and the mixture extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc = 95:5) to give **40** (1.471 g, 74%) as a colorless oil; EI-MS $m/z = 289$ [M^+]; TLC: $R_f = 0.67$ (petroleum ether/EtOAc = 1:1); IR (film): *v* 3063–2793, 1746, 1454, 1270, 1181, 1029, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.88 (t, 3H, $J = 7.0$ Hz, $CH_2CH_2CH_2C\underline{H}_3$), 1.27 (m, 9H, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$, $CO_2CH_2C\underline{H}_3$), 1.75 (ddd, 1H, $J = 12.6$, 9.6, 7.9 Hz, H-3a), 2.01 (dd, 1H, $J = 8.8$, 8.8 Hz, H-5a), 2.14 (ddd, 1H, $J = 12.6$, 9.0, 5.9 Hz, H-3b), 2.26 (m, 1H, H-4), 3.16 (dd, 1H, $J = 8.8$, 6.9 Hz, H-5b), 3.28 (dd, 1H, $J = 9.6$, 5.9 Hz, H-2), 3.53 (d, 1H, $J = 12.7$ Hz, NCH_2Ph), 3.93 (d, 1H, $J = 12.7$ Hz, NCH_2Ph), 4.14 (m, 2H, $CO_2C\underline{H}_2CH_3$), 7.21–7.41 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 62.90 MHz): δ 13.97 ($CH_2CH_2CH_2\underline{C}H_3$), 14.24 ($CO_2CH_2\underline{C}H_3$), 22.73, 31.91, 34.84 ($\underline{C}H_2\underline{C}H_2\underline{C}H_2CH_3$), 36.55 (C-3), 36.90 (C-4), 59.17 ($N\underline{C}H_2Ph$), 60.03 ($CO_2\underline{C}H_2CH_3$), 60.47 (C-5), 65.19 (C-2), 127.03, 128.14, 129.22, 138.42 (C-Ar); Anal. calcd for $C_{18}H_{27}NO_2$ (289.42): C, 74.70; H, 9.40; N, 4.84, found: C, 75.19; H, 9.62; N, 4.73; $[\alpha]_D^{20} = +59.0$ (*c* 1.0, $CHCl_3$).

***ent*-40** $[\alpha]_D^{20} = -56.5$ (*c* 1.0, $CHCl_3$) was prepared under the same reaction conditions as described for **40**, starting from ***ent*-38**.

4.32. (2*R*,4*S*)-5-(1-Benzyl-4-butylpyrrolidin-2-yl)nonan-5-ol 41

To a suspension of Cu(I)I (120 mg, 0.63 mmol) in Et_2O (10 mL) was added a solution of n-BuLi (0.73 mL, 1.6 M in hexane) at −30°C and the mixture stirred for 30 min **38** (36.5 mg, 0.09 mmol), dissolved in Et_2O was then added and the mixture warmed up to −20°C. After 1 h, the reaction was quenched with an aqueous solution of $NaHCO_3$ and the mixture extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated. The resulting residue was purified by flash chromatography (petroleum ether/EtOAc = 99:1) to give **41** (24.1 mg, 74%) as a white crystalline solid. Mp: 275°C; EI-MS $m/z = 302$ ([$M-C_4H_9$]$^+$); TLC: $R_f = 0.72$ (petrolether/ethylacetat, 1:1); IR (KBr): *v* 3500, 3027–2791, 1713, 1494, 1454, 1376, 1132, 1027, 996, 909, 732, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.81–1.63 (m,

19H, H-3a/C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_3$), 1.94 (dd, 1H, J=9.3, 9.3 Hz, H-5a), 2.04 (m, 2H, H-3b/H-4), 2.90 (dd, 1H, J=9.8, 2.2 Hz, H-2), 3.03 (brdd, 1H, J=9.3, 6.3 Hz, H-5b), 3.50 (d, 1H, J=13.4 Hz, NC$\underline{H}_2$Ph), 4.18 (d, 1H, J=13.4 Hz, NC$\underline{H}_2$Ph), 7.21–7.41 (m, 5H, Ar); Anal. calcd for $C_{24}H_{41}NO$ (359.60): C, 80.16; H, 11.49; N, 3.90, found: C, 80.04; H, 11.42; N, 4.00; $[\alpha]_D^{20}$=+16.1 (*c* 0.32, $CHCl_3$).

4.33. (2*R*,4*S*)-1-Benzyl-4-methylpyrrolidin-2-carboxylic acid hydrochloride 42

To **39** (110 mg, 0.44 mmol) was added 5 M HCl (4 mL) after which the mixture was stirred for 48 h at 60°C. The mixture was then evaporated to leave pure **42** (1136 mg, 99%) as a white solid. Mp: 240–242°C; IR (film): *v* 3367–2927, 1712, 1662, 1457, 1357, 1207, 1025, 752, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 1.05 (d, 3H, J=6.3 Hz, CH_3), 2.15 (m, 1H, H-3a), 2.31 (m, 2H, H-3b/H-4), 2.93 (dd, 1H, J=11.1, 10.3 Hz, H-5a), 3.65 (dd, 1H, J=11.1, 6.2 Hz, H-5b), 4.39 (m, 3H, NC$\underline{H}_2$Ph/NC$\underline{H}_2$Ph/H-2), 7.40–7.55 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 90.56 MHz): δ 16.61 (CH_3), 32.16 (C-4), 36.81 (C-3), 59.68 (NC$\underline{H}_2$Ph), 61.64 (C-5), 67.63 (C-2), 130.25, 130.72, 131.13, 131.68 (C-Ar), 173.41 (COOH); Anal. calcd for $C_{13}H_{17}NO_2$×0.25 H_2O (255.10): C, 60.09; H, 7.18; N, 5.39, found: C, 59.80; H, 7.58; N, 5.16; $[\alpha]_D^{20}$=+33.9 (*c* 1.0, $CHCl_3$).

***ent*-42** $[\alpha]_D^{20}$=−33.7 (*c* 0.74, $CHCl_3$) was prepared under the same reaction conditions as described for **42**, starting from ***ent*-39**.

4.34. (2*R*,4*S*)-1-Benzyl-4-butylpyrrolidin-2-carboxylic acid hydrochloride 43

A mixture of **40** (63.8 mg, 0.22 mmol) and 5 M HCl (4 mL) was reacted and worked up as described for **42** to leave pure **43** (64.9 mg, 99%) as a white solid. Mp: 198–202°C; EI-MS m/z=261 [M$^+$], 216 (α-cleavage, -HCl); IR (film): *v* 2954–2391, 1712, 1457, 1357, 1207, 998, 817, 752, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 0.80 (t, 3H, J=6.7 Hz, $CH_2CH_2CH_2C\underline{H}_3$), 1.31 (m, 6H, C$\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 2.22 (m, 3H, H-3a/H-3b/H-4), 2.94 (dd, 1H, J=11.0, 11.0 Hz, H-5a), 3.65 (dd, 1H, J=11.0, 6.3 Hz, H-5b), 4.28 (m, 1H, H-2), 4.34 (d, 1H, J=12.8 Hz, NC$\underline{H}_2$Ph), 4.43 (d, 1H, J=12.8 Hz, NC$\underline{H}_2$Ph), 7.40–7.55 (m, 5H, Ar); Anal. calcd for $C_{16}H_{23}NO_2$ x HCl (297.83): C, 64.53; H, 8.12; N, 4.70, found: C, 64.50; H, 7.98; N, 4.93; $[\alpha]_D^{20}$=+37.1 (*c* 0.85, $CHCl_3$).

***ent*-43** was prepared under the same reaction conditions as described for **43**, starting from ***ent*-40**.

4.35. (3*R*,5*R*)-1-Benzyl-5-hydroxymethylpyrrolidin-3-yl tosylate 44

A mixture of **38** (2.8 g, 7.01 mmol) and $LiAlH_4$ (14.0 mL, 1 M solution in THF) in THF (30 mL) were reacted and worked up as described for **19** to give **44** (2.33 g, 92%) as a white crystalline solid. Mp: 40–41°C; EI-MS m/z=361 [M$^+$]; TLC: R_f=0.2 (petroleum ether/EtOAc=1:1); IR (film): *v* 3432, 3062–2803, 1596, 1357, 1176, 948, 898, 752, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): 2.00 (ddd, 1H, J=15.1, 6.9, 1.9 Hz, H-4a), 2.19 (ddd, 1H, J=15.1, 8.7, 6.9 Hz, H-4b), 2.35 (s, 3H, $OSO_2C_6H_4C\underline{H}_3$), 2.38 (dd, 1H, J=11.7, 4.5 Hz, H-2a), 2.64 (m, 1H, H-5), 3.02 (brd, 1H, J=11.7 Hz, H-2b), 3.19 (d, 1H, J=13.4 Hz, NC$\underline{H}_2$Ph), 3.35 (dd, 1H, J=11.4 Hz, C$\underline{H}_2$OH), 3.65 (brd, 1H, J=11.4 Hz, C$\underline{H}_2$OH), 3.91 (d, 1H, J=13.4 Hz, NC$\underline{H}_2$Ph), 4.88 (m, 1H, H-3), 7.20–7.67 (m, 7H, Ar/$OSO_2C_6\underline{H}_4CH_3$), 7.74 (m, 2H, $OSO_2C_6\underline{H}_4CH_3$); Anal. calcd for $C_{19}H_{23}NO_4S$ (361.46): C, 63.14; H, 6.41; N, 3.87; S, 8.87, found: C, 63.18; H, 6.34; N, 3.86; S, 8.82; $[\alpha]_D^{20}$=+38.9 (*c* 1.0, $CHCl_3$).

***ent*-44** was prepared under the same reaction conditions as described for **44**, starting from ***ent*-38**.

4.36. (3*R*,5*R*)-1-Benzyl-5-(*tert*-butyldimethylsilyloxymethyl)pyrrolidin-3-yl tosylate 45

A solution of **44** (183 mg, 0.51 mmol) in DMF (15 mL), imidazole (138 mg, 2.02 mmol) and TBSCl (153 mg, 1.01 mmol) were reacted and worked up (petroleum ether/EtOAc=1:1) as described for **10** to give **45** (228 mg, 95%) as a yellowish solid. Mp: 50–57°C; EI-MS m/z=344 ([M−OTBS]$^+$); TLC: R_f=0.68 (petroleum ether/EtOAc=1:1); IR (film): *v* 3062–2800, 1600, 1465, 1361, 1253, 1176, 1099, 898, 775, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 0.02 (s, 6H, OSi(C$\underline{H}_3$)$_2$*t*Bu), 0.86 (s, 9H, OSi(CH$_3$)$_2$*t*$\underline{Bu}$), 1.82 (brdd, 1H, J=13.9, 6.7 Hz, H-4a), 2.27 (ddd, 1H, J=13.9, 7.6, 7.6 Hz, H-4b), 2.35 (dd, 1H, J=11.7, 5.1 Hz, H-2a), 2.42 (s, 3H, $OSO_2C_6H_4C\underline{H}_3$), 2.67 (m, 1H, H-5), 2.96 (brd, 1H, J=11.7 Hz, H-2b), 3.32 (d, 1H, J=13.4 Hz, NC$\underline{H}_2$Ph), 3.51 (dd, 1H, J=10.0, 6.7 Hz, C$\underline{H}_2$OTBS), 3.70 (dd, 1H, J=10.0, 5.5 Hz, C$\underline{H}_2$OTBS), 4.09 (d, 1H, J=13.4 Hz, NC$\underline{H}_2$Ph), 4.92 (m, 1H, H-3), 7.20–7.31 (m, 7H, Ar/$OSO_2C_6\underline{H}_4CH_3$), 7.72 (m, 2H, $OSO_2C_6\underline{H}_4CH_3$); Anal. calcd for $C_{25}H_{37}NO_4SSi$ (475.73): C, 63.12; H, 7.84; N, 2.94; S, 6.74, found: C, 63.06; H, 7.67; N, 2.88; S, 6.58; $[\alpha]_D^{20}$=+76.7 (*c* 1.0, $CHCl_3$).

***ent*-45** was prepared under the same reaction conditions as described for **45**, starting from ***ent*-44**.

4.37. (2*R*,4*S*)-1-Benzyl-2-(*tert*-butyldimethylsilyloxymethyl)-4-methylpyrrolidine 46

To a solution of **45** (310 mg, 0.65 mmol) in Et_2O (30 mL) was added MeMgBr (0.43 mL, 3 M in Et_2O) at 0°C. The solution was stirred for 90 min at 0°C and another 5 h at rt, after which an aqueous saturated solution of NH_4Cl was added and the resulting mixture extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc=9:1) to leave **46** (156.6 mg, 75%) as a colorless liquid; EI-MS m/z=319 [M$^+$]; TLC: R_f=0.29 (petroleum ether/EtOAc=9:1); IR (film): *v* 3085–2807, 1465, 1369, 1253, 964, 836, 775, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz): δ 0.02 (s, 6H, OSi(C$\underline{H}_3$)$_2$*t*Bu), 0.87 (s, 9H, OSi(CH$_3$)$_2$*t*$\underline{Bu}$), 0.94 (d, 3H, J=6.4 Hz, CH_3), 1.39 (m,

1H, H-3a), 1.66 (m, 1H, H-5a), 1.97 (m, 2H, H-3b/H-5b), 2.96 (m, 1H, H-4), 3.16 (m, 1H, H-2), 3.47 (m, 2H, $C\underline{H}_2OSi(CH_3)_2tBu/C\underline{H}_2OSi(CH_3)_2tBu$), 3.71 (d, 1H, $J=14.2$ Hz, NCH_2Ph), 3.93 (d, 1H, $J=14.2$ Hz, NCH_2Ph), 7.20–7.38 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 360 MHz): δ 16.12, 18.22, 22.06 (C-Tbs), 25.91 (C-CH_3), 26.33 (C-5), 31.32 (C-3), 52.57 (NCH_2Ph), 56.26 (C-2), 61.66 (C-4), 65.57 (C-CH_2), 126.54, 128.10, 128.40, 132.12 (C-Ar); Anal. Calcd for $C_{19}H_{33}NOSi$ (319.57): C, 71.41; H, 10.41; N, 4.38, found: C, 71.57; H, 10.56; N, 4.25; $[\alpha]_D^{20}=+63.2$ (c 0.85, $CHCl_3$).

4.38. (2*R*,4*S*)-1-Benzyl-2-(*tert*-butyldimethylsilyloxymethyl)-4-propylpyrrolidine 47

To a solution of **45** (276 mg, 0.58 mmol) in Et_2O (30 mL) was added PrMgCl (0.58 mL, 2 M in Et_2O) at 0°C. After stirring for 90 min at 0°C and for a further 3h at rt, the mixture was worked up as described for **46** to leave **47** (95.8 mg, 75%) as a colorless oil; EI-MS $m/z=347$ [M^+]; TLC: $R_f=0.38$ (petroleum ether/EtOAc=98:2); IR (film): ν 3062–2803, 1461, 1361, 1253, 1099, 836, 775, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.01 (s, 6H, $OSi(C\underline{H}_3)_2tBu$), 0.86 (m, 12H, $OSi(CH_3)_2t\underline{Bu}/CH_2CH_2C\underline{H}_3$), 1.14 (m, 2H, $CH_2CH_2CH_3$), 1.32 (m, 1H, $CH_2CH_2CH_3$), 1.52 (m, 2H, H-3a/$CH_2CH_2CH_3$), 1.67 (m, 1H, H-5a), 1.91 (m, 2H, H-5b/H-3b), 2.98 (m, 2H, H-2/H-4), 3.48 (m, 2H, $C\underline{H}_2OSi(CH_3)_2tBu/C\underline{H}_2OSi(CH_3)_2tBu$), 3.77 (d, 1H, $J=14.2$ Hz, NCH_2Ph), 3.92 (d, 1H, $J=14.2$ Hz, NCH_2Ph), 7.20–7.37 (m, 5H, Ar); Anal. calcd for $C_{21}H_{37}NOSi$ (347.62): C, 72.56; H, 10.73; N, 4.03, found: C, 72.33; H, 10.76; N, 4.07; $[\alpha]_D^{20}=+39.5$ (c 0.41, $CHCl_3$).

4.39. (2*R*,4*S*)-1-Benzyl-4-methylpyrrolidine-2-carboxamide 48

A solution of NH_3-saturated MeOH (20 mL) and **39** (216 mg, 0.87 mmol) were reacted and worked up as described for **2**. The resulting residue was purified by flash chromatography (petroleum ether/EtOAC=7:3, then CH_2Cl_2/MeOH=1:1) to give pure **48** (178.3 mg, 94%) as a white crystalline solid. Mp: 68–70°C; EI-MS $m/z=218$ [M^+]; TLC: $R_f=0.03$ (petroleum ether/EtOAc=7:3); IR (film): ν 3424, 3255, 3062–2723, 1681, 1454, 1373, 1319, 1130, 752, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): 0.98 (d, 3H, $J=6.5$ Hz, $C\underline{H}_3$), 1.83 (ddd, 1H, $J=12.8$, 10.6, 10.4 Hz, H-3a), 2.01 (dd, 1H, $J=10.3$, 8.6 Hz, H-5a), 2.09 (ddd, 1H, $J=12.8$, 8.6, 4.1 Hz, H-3b), 2.18 (m, 1H, H-4), 3.07 (dd, 1H, $J=8.6$, 5.7 Hz, H-5b), 3.28 (dd, 1H, $J=10.6$, 4.1 Hz, H-2), 3.49 (d, 1H, $J=12.7$ Hz, NCH_2Ph), 3.92 (d, 1H, $J=12.7$ Hz, NCH_2Ph), 5.27 (brs, 1H, NH_2), 7.20–7.39 (m, 6H, Ar/NH_2); Anal. calcd for $C_{13}H_{18}N_2O$ (218.30): C, 71.53; H, 8.31; N, 12.83, found: C, 71.58; H, 8.31; N, 12.80; $[\alpha]_D^{20}=+74.9$ (c 0.7, $CHCl_3$).

***ent*-48** $[\alpha]_D^{20}=-69.3$ (c 0.67, $CHCl_3$) was prepared under the same reaction conditions as described for **33**, starting from ***ent*-39**.

4.40. (2*R*,4*S*)-1-Benzyl-4-butylpyrrolidine-2-carboxamide 49

A solution of NH_3-saturated MeOH (30 mL) and **40** (228 mg, 0.79 mmol) were reacted and worked up as described for **2**. The resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH=9:1) to give pure **49** (136 mg, 66%) as opaque crystals. Mp: 89–90°C; EI-MS $m/z=260$ [M^+]; TLC: $R_f=0.04$ (petroleum ether/EtOAc=7:3); IR (film): ν 3424, 3185, 3062–2800, 1677, 1573, 1454, 1373, 1311, 1261, 1029, 802 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.35 (t, 3H, $J=7.0$ Hz, $CH_2CH_2CH_2C\underline{H}_3$), 1.25 (m, 6H,$C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 1.84 (m, 1H, H-3a), 2.05 (m, 3H, H-5a/H-3b/H-4), 3.09 (dd, 1H, $J=8.9$, 5.5 Hz, H-5b), 3.24 (dd, $J=10.6$, 3.8 Hz, H-2), 3.47 (d, 1H, $J=12.7$ Hz, NCH_2Ph), 3.92 (d, 1H, $J=12.7$ Hz, NCH_2Ph), 5.57 (brs, 1H, NH_2), 7.25–7.36 (m, 6H, Ar/NH_2); Anal. calcd for $C_{16}H_{24}N_2O$ (260.38): C, 73.81; H, 9.29; N, 10.76, found: C, 73.86; H, 9.27; N, 10.64; $[\alpha]_D^{20}=+82.3$ (c 1.0, $CHCl_3$).

***ent*-49** $[\alpha]_D^{20}=-79.7$ (c 1.0, $CHCl_3$) was prepared under the same reaction conditions as described for 34, starting from ***ent*-40**.

4.41. (2*R*,4*S*)-(1-Benzyl-4-methylpyrrolidin-2-yl)methylamine 50

A solution of **48** (29.2 mg, 0.13 mmol) in Et_2O (10 mL) and $LiAlH_4$ (0.54 mL, 1 M solution in Et_2O) were reacted (reaction time: 24 h) and worked up (extraction was performed with CH_2Cl_2, flash chromatography was not necessary) as described for **4** to leave pure **50** (23.2 mg, 85%) as a weakly yellowish oil; EI-MS $m/z=174$ (α-cleavage, [$M-CH_2NH_2]^+$); IR (film): ν 3062–2788, 1577, 1454, 1261, 1025, 798, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.96 (d, 3H, $J=7.0$ Hz, CH_3), 1.49 (m, 1H, H-3a), 1.85 (m, 2H, H-3b/H-5a), 2.14 (m, 1H, H-4), 2.70 (m, 3H, CH_2NH_2/CH_2NH_2/H-2), 3.00 (dd, 1H, $J=8.5$, 6.4 Hz, H-5b), 3.30 (d, 1H, $J=13.1$ Hz, NCH_2Ph), 3.95 (d, 1H, $J=13.1$ Hz, NCH_2Ph), 7.22–7.34 (m, 5H, Ar); HR-EIMS: 174.12812 (Anal. calcd for $C_{12}H_{16}N$: 174.12828); $[\alpha]_D^{20}=+70.4$ (c 0.13, $CHCl_3$).

***ent*-50** $[\alpha]_D^{20}=-75.0$ (c 0.025, $CHCl_3$) was prepared under the same reaction conditions as described for **4**, starting from ***ent*-48**.

4.42. (2*R*,4*S*)-(1-Benzyl-4-butylpyrrolidin-2-yl)methylamine 51

A mixture of **49** (25.1 mg, 0.10 mmol) and $LiAlH_4$ (0.39 mL, 1 M solution in Et_2O) in Et_2O (10 mL) was reacted and worked up as described for **4**. Pure **51** (22.8 mg, 96%) was obtained as a yellowish oil without further purification; EI-MS $m/z=216$ (α-cleavage, [$M-CH_2NH_2]^+$); TLC: $R_f=0.07$ (CH_2Cl_2/MeOH=9:1); IR (film): ν 3062–2792, 1673, 1577, 1454, 1261, 1025, 798, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.95 (t, 3H, $J=7.0$ Hz, $CH_2CH_2CH_2CH_3$), 1.35 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.53 (m, 1H, H-3a), 1.91 (m, 2H,

H-3b/H-5a), 2.12 (m, 1H, H-4), 2.75 (m, 2H, CH_2NH_2/H-2), 2.84 (dd, 1H, $J=12.3$, 5.5 Hz, CH_2NH_2), 3.12 (dd, 1H, $J=8.2$, 6.5 Hz, H-5b), 3.38 (d, 1H, $J=13.0$ Hz, NCH_2Ph), 4.04 (d, 1H, $J=13.0$ Hz, NCH_2Ph), 7.28–7.48 (m, 5H, Ar); HR-EIMS: 216.17558 (Anal. calcd for $C_{15}H_{22}N$: 216.17523); $[\alpha]_D^{20}=+84.0$ (c 0.08, $CHCl_3$).

***ent*-51** $[\alpha]_D^{20}=-80.0$ (c 0.09, $CHCl_3$) was prepared under the same reaction conditions as described for **51**, starting from ***ent*-49**.

4.43. (2*R*,4*S*)-(1-Benzyl-4-methylpyrrolidin-2-yl)-methanol 52

A solution of **39** (585 mg, 2.4 mmol) in THF (50 mL) and $LiAlH_4$ (4.73 mL, 1 M solution in THF) were reacted (reaction time: 1 h) and worked up as described for **20** to give **52** (444.7 mg, 92%) as a colorless oil; EI-MS $m/z=205$ [M^+]; TLC: $R_f=0.28$ (CH_2Cl_2/MeOH = 9:1); IR (film): ν 3388, 3027–2780, 1454, 1375, 1028, 746, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.95 (d, 3H, $J=6.4$ Hz, CH_3), 1.54 (ddd, 1H, $J=12.7$, 9.5, 9.5 Hz, H-3a), 1.97 (m, 2H, H-3b/H-5a), 2.14 (m, 1H, H-4), 2.83 (m, 1H, H-2), 3.03 (dd, 1H, $J=8.5$, 6.0 Hz, H-5b), 3.36 (d, 1H, $J=13.1$ Hz, NCH_2Ph), 3.39 (dd, 1H, $J=10.7$, 2.1 Hz, CH_2OH), 3.62 (dd, 1H, $J=10.7$, 3.4 Hz, CH_2OH), 3.94 (d, 1H, $J=13.1$ Hz, NCH_2Ph), 7.22–7.35 (m, 5H, Ar); Anal. calcd for $C_{13}H_{19}NO$ (205.30): C, 76.06; H, 9.33; N, 6.82, found: C, 75.86; H, 9.27; N, 6.87; $[\alpha]_D^{20}=+63.5$ (c 1.0, $CHCl_3$).

***ent*-52** $[\alpha]_D^{20}=-65.1$ (c 0.98, $CHCl_3$) was prepared under the same reaction conditions as described for **52**, starting from ***ent*-39**.

4.44. (2*R*,4*S*)-(1-Benzyl-4-butylpyrrolidin-2-yl)methanol 53

A solution of **40** (686 mg, 2.37 mmol) in THF (50 mL) and $LiAlH_4$ (4.74 mL, 1 M solution in THF) were reacted and worked up (eluent for flash chromatography: CH_2Cl_2/MeOH = 9:1, extraction with CH_2Cl_2) as described for **19** to leave pure **53** (575 mg, 98%) as an opaque solid. Mp: 58°C; EI-MS $m/z=216$ (α-cleavage); TLC: $R_f=0.36$ (CH_2Cl_2/MeOH = 9:1); IR (film): ν 3401, 3085–2792, 1604, 1454, 1133, 1033, 971, 917, 748, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.85 (t, 3H, $J=7.0$ Hz, $CH_2CH_2CH_2CH_3$), 1.24 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.55 (m, 1H, H-3a), 1.97 (m, 3H, H-5a, H-4, H-3b), 2.80 (m, 1H, H-2), 3.05 (dd, 1H, $J=8.5$, 6.2 Hz, H-5b), 3.34 (d, 1H, $J=13.0$ Hz, NCH_2Ph), 3.39 (dd, 1H, $J=10.7$, 1.7 Hz, CH_2OH), 3.63 (dd, 1H, $J=10.7$, 3.3 Hz, CH_2OH), 3.94 (d, 1H, $J=13.0$ Hz, NCH_2Ph), 7.19–7.37 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 90.56 MHz): δ 13.98 ($CH_2CH_2CH_2CH_3$), 22.79, 30.54, 34.00 ($CH_2CH_2CH_2CH_3$), 35.07 (C-3), 37.50 (C-4), 58.73 (NCH_2Ph), 60.98 (C-5), 62.18 (CH_2OH), 64.25 (C-2), 127.15, 128.36, 128.80, 138.91 (C-Ar); Anal. calcd for $C_{16}H_{25}NO$ (247.38): C, 77.68; H, 10.19; N, 5.66, found: C, 77.61; H, 10.09; N, 5.65; $[\alpha]_D^{20}=+78.0$ (c 1.0, $CHCl_3$).

***ent*-53** $[\alpha]_D^{20}=-85.3$ (c 0.23, $CHCl_3$)) was prepared under the same reaction conditions as described for **53**, starting from ***ent*-40**.

4.45. (2*R*,4*S*)-1-Benzyl-4-methyl-2-chloromethylpyrrolidine hydrochloride 54

A solution of **52** (405 mg, 1.98 mmol) in $CHCl_3$ (25 mL) and $SOCl_2$ (0.22 mL, 2.97 mmol) were reacted (reaction time: 24 h) and worked up as described for **55** to leave crude **54**. Crude **54** was used for the next reaction without further purification.

***ent*-54** was prepared under the same reaction conditions as described for **54**, starting from ***ent*-52**.

4.46. (2*R*,4*S*)-1-Benzyl-4-butyl-2-chloromethylpyrrolidine hydrochloride 55

To a solution of **53** (113 mg, 0.46 mmol) in $CHCl_3$ (20 mL) was added $SOCl_2$ (0.07 mL, 0.92 mmol) with the resulting mixture refluxed for 4 h. After cooling to rt, the mixture was evaporated to leave pure **55** (135 mg, 98%) as a weakly yellowish solid. Mp: 185–190°C; EI-MS $m/z=265$ [M^+]; TLC: $R_f=0.83$ (CH_2Cl_2/MeOH = 9:1); IR (film): ν 3062–2857, 2468, 1457, 1261, 1025, 752, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.80 (t, 3H, $J=6.9$ Hz, $CH_2CH_2CH_2CH_3$), 1.22 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.82 (ddd, 1H, $J=13.6$, 10.0, 10.0 Hz, H-3a), 2.22 (ddd, 1H, $J=13.6$, 7.8, 6.0 Hz, H-3b), 2.40 (dd, 1H, $J=18.8$, 10.6 Hz, H-5a), 2.56 (m, 1H, H-4), 3.58 (m, 2H, H-5b/H-2), 3.87 (m, 2H, NCH_2Ph/NCH_2Ph), 4.15 (dd, 1H, $J=13.1$, 5.3 Hz, CH_2Cl), 4.31 (dd, 1H, $J=13.1$, 5.0 Hz, CH_2Cl), 7.11–7.68 (m, 5H, Ar); Anal. calcd for $C_{16}H_{24}ClN\times HCl$ (302.14): C, 63.57; H, 8.34; N, 4.63, found: C, 63.80; H, 9.03; N, 4.16; $[\alpha]_D^{20}=+24.8$ (c 0.61, $CHCl_3$).

***ent*-55** $[\alpha]_D^{20}=-29.3$ (c 0.2, $CHCl_3$) was prepared under the same reaction conditions as described for **55**, starting from ***ent*-53**.

4.47. (2*R*,4*S*)-(1-Benzyl-4-methylpyrrolidin-2-yl)-acetonitrile 56 and (2*S*,4*S*)-(1-benzyl-4-methylpyrrolidin-2-yl)acetonitrile 60

To a solution of **54** (443 mg, 1.98 mmol) in 80% EtOH (20 mL) was added NaCN (1.94 g, 39.5 mmol) and the mixture refluxed for 48 h. After cooling to rt, an aqueous saturated solution of $NaHCO_3$ was added and the mixture extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by flash chromatography (petroleum ether/EtOAc = 9:1) to give **56** and **60** (overall yield: 209 mg, 49%, two steps).

Analytical data of **56**: EI-MS $m/z=174$ (α-cleavage, [M-CH_2CN]$^+$); TLC: $R_f=0.42$ (petroleum ether/EtOAc = 8:2); IR (film): ν 3027–2796, 2248, 1454, 1373, 1133, 1060, 744, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.98 (d, 3H, $J=6.7$ Hz, CH_3), 1.69 (ddd, 1H, $J=12.9$, 9.1, 9.1 Hz, H-3a), 1.92 (m, 2H, H-3b/H-5a), 2.35 (m, 3H, H-4/CH_2CN/CH_2CN), 2.94 (m, 1H, H-2),

3.07 (dd, 1H, $J=8.9$, 6.4 Hz, H-5b), 3.49 (d, 1H, $J=12.9$ Hz, NCH_2Ph), 3.87 (d, 1H, $J=12.9$ Hz, NCH_2Ph), 7.24–7.34 (m, 5H, Ar); Anal. calcd for $C_{14}H_{18}N_2$ (214.31): C, 78.46; H, 8.47; N, 13.07, found: C, 78.46; H, 8.47; N, 13.07; $[\alpha]_D^{20}=-72.6$ (*c* 0.6, $CHCl_3$).

***ent*-56** $[\alpha]_D^{20}=+95.6$ (*c* 0.3, $CHCl_3$) was prepared under the same reaction conditions as described for **56**, starting from ***ent*-54**.

4.48. (2*R*,4*S*)-(1-Benzyl-4-butylpyrrolidin-2-yl)-acetonitrile 57 and (2*S*,4*S*)-(1-benzyl-4-butylpyrrolidin-2-yl)acetonitrile 61

A solution of **55** (83.5 mg, 0.31 mmol) in 80% EtOH (10 mL) and NaCN (307 mg, 6.26 mmol) were reacted and worked up (petroleum ether/EtOAc = 95:5) as described for **23** to give **57** and **61** (overall yield: 51.3 mg, 72%, two steps). Compound **57** could be isolated as a yellowish, creamy mass; EI-MS $m/z=216$ (α-cleavage, $[M-CH_2CN]^+$); TLC: $R_f=0.2$ (petroleum ether/EtOAc = 95:5); IR (film): *v* 3085–2800, 2248, 1731, 1454, 1373, 1214, 1141, 755, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.86 (t, 3H, $J=7.0$ Hz, $CH_2CH_2CH_2C\underline{H}_3$), 1.26 (m, 6H, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 1.72 (ddd, 1H, $J=13.0$, 9.1, 9.1 Hz, H-3a), 1.88 (ddd, 1H, $J=13.0$, 8.5, 4.9 Hz, H-3b), 1.95 (dd, 1H, $J=9.4$, 9.4 Hz, H-5a), 2.21 (m, 1H, H-4), 2.32 (dd, 1H, $J=16.7$, 6.5 Hz, CH_2CN), 2.39 (dd, 1H, $J=16.7$, 4.3 Hz, CH_2CN), 2.91 (m, 1H, H-2), 3.08 (dd, 1H, $J=9.4$, 6.5 Hz, H-5b), 3.47 (d, 1H, $J=13.0$ Hz, NCH_2Ph), 3.87 (d, 1H, $J=13.0$ Hz, NCH_2Ph), 7.24–7.35 (m, 5H, Ar); Anal. calcd for $C_{17}H_{24}N_2$ (256.39): C, 79.64; H, 9.44; N, 10.93, found: C, 79.68; H, 9.39; N, 10.70; $[\alpha]_D^{20}=+41.4$ (*c* 0.1, $CHCl_3$).

***ent*-57** $[\alpha]_D^{20}=-43.0$ (*c* 0.5, $CHCl_3$) was prepared under the same reaction conditions as those described for **57** starting from ***ent*-55**.

4.49. (2*R*,4*S*)-2-(1-Benzyl-4-methylpyrrolidin-2-yl)-ethylamine 58

A solution of **56** (6.9 mg, 0.03 mmol) in THF (5 mL) and $LiAlH_4$ (0.07 mL, 1 M solution in THF) were reacted and worked up as described for **20** to leave crude **56**. Crude **56** was used for the next reaction without further purification.

4.50. (2*R*,4*S*)-2-(1-Benzyl-4-butylpyrrolidin-2-yl)-ethylamine 59

A mixture of **56** (10.7 mg, 0.04 mmol) and $LiAlH_4$ (0.08 mL, 1 M solution in THF) in THF (10 mL) were reacted and worked up as described for **19** to leave crude **59**. Crude **59** was used for the next reaction step without further purification.

***ent*-59** was prepared under the same reaction conditions as described for **59**, starting from ***ent*-56**.

4.51. (2*R*,4*R*)-*N*-[(1-Benzyl-4-hydroxypyrrolidin-2-yl)methyl]-5-chloro-2-methoxy-4-methylaminobenzamide 62

A suspension of 5-chloro-2-methoxy-4-(methylamino)benzoic acid (42.0 mg, 0.19 mmol), HOBt (26.8 mg, 0.18 mmol) and DCC (36.7 mg, 0.18 mmol) in EtOAc (15 mL) was reacted and worked up (gradient: CH_2Cl_2/MeOH = 98:2 to 94:6) as described for ***ent*-63** to give **62** (58.2 mg, 89%) as an opaque, yellowish solid. Mp: 50–51°C; TLC: $R_f=0.20$ (CH_2Cl_2/MeOH = 9:1); IR (film): *v* 3356, 3062–2800, 1627, 1515, 1333, 1281, 1245, 1214, 1154, 1135, 1035, 911, 809, 731, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 1.66 (brdd, 1H, $J=14.0$, 6.0 Hz, H-3a), 2.36 (m, 2H, H-3b/H-5a), 2.83 (m, 1H, H-2), 2.95 (brd, 3H, $J=5.3$ Hz, $NHC\underline{H}_3$), 3.27 (d, 1H, $J=12.8$ Hz, NCH_2Ph), 3.39 (brd, 1H, $J=12.8$ Hz, H-5b), 3.91 (m, 5H, $C\underline{H}_2NH/C\underline{H}_2NH/OC\underline{H}_3$), 4.09 (d, 1H, $J=12.8$ Hz, NCH_2Ph), 4.14 (m, 1H, H-4), 4.73 (m, 1H, $N\underline{H}CH_3$), 6.12 (s, 1H, $C\underline{H}COCH_3$), 7.22–7.36 (m, 5H, Ar), 8.14 (s, 1H, $C\underline{H}CCl$), 8.25 (brd, 1H, $J=7.8$ Hz, $N\underline{H}CH_2$); Anal. calcd for $C_{21}H_{26}ClN_3O_3$ (403.91): C, 62.45; H, 6.49; N, 10.40, found: C, 62.36; H, 6.54; N, 10.42; $[\alpha]_D^{20}=+47.2$ (*c* 0.62, $CHCl_3$).

***ent*-62** was synthesized under the same reaction conditions, starting from **5**; $[\alpha]_D^{20}=-79.4$ (*c* 0.41, $CHCl_3$).

4.52. (2*S*,4*R*)-*N*-[(1-Benzyl-4-hydroxypyrrolidin-2-yl)-methyl]-5-chloro-2-methoxy-4-methylaminobenzamide *ent*-63

A suspension of 5-chloro-2-methoxy-4-(methylamino)benzoic acid (44.75 mg, 0.21 mmol), HOBt (28.59 mg, 0.189 mmol) and DCC (38.97 mg, 0.19 mmol) in EtOAc (15 mL) was stirred at rt for 15 min. Compound **4** (35.5 mg, 0.17 mmol), dissolved in EtOAc, was then added and stirring continued for a further 24 h. The mixture was filtered through Celite and the filtrate was evaporated. The residue was purified by flash chromatography (CH_2Cl_2/MeOH = 95:5) to give ***ent*-63** (36.7 mg, 53%) as a glutinous, colorless mass; TLC: $R_f=0.07$ (CH_2Cl_2/MeOH = 9:1); IR (film): *v* 3363, 3027–2803, 1601, 1516, 1333, 1280, 1246, 1213, 1036, 910, 809, 731, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 1.89 (m, 1H, H-3a), 2.01 (ddd, 1H, $J=13.8$, 7.1, 7.1 Hz, H-3b), 2.39 (m, 1H, H-5a), 2.96 (d, 3H, $J=5.0$ Hz, $NHC\underline{H}_3$), 3.28 (m, 2H, H-5b/H-2), 3.39 (brd, 1H, $J=14.2$ Hz, $C\underline{H}_2NH$), 3.47 (d, 1H, $J=12.7$ Hz, NCH_2Ph), 3.85 (m, 4H, $OC\underline{H}_3/C\underline{H}_2NH$), 4.11 (d, 1H, $J=12.7$ Hz, NCH_2Ph), 4.34 (m, 1H, H-4), 4.73 (m, 1H, $N\underline{H}CH_3$), 6.12 (s, 1H, $C\underline{H}COCH_3$), 7.20–7.39 (m, 5H, Ar), 8.12 (s, 1H, $C\underline{H}CCl$), 8.27 (brd, 1H, $J=6.0$ Hz, $N\underline{H}CH_2$); ^{13}C NMR ($CDCl_3$, 62.89 MHz): δ 30.19 ($NHC\underline{H}_3$), 38.45 (C-3), 40.19 ($\underline{C}H_2NH$), 55.87 ($O\underline{C}H_3$), 58.51 (NCH_2Ph), 62.02 (C-5/C-2), 70.11 (C-4), 93.04 ($\underline{C}HCOCH_3$), 127.15, 128.31, 128.79 (C-Ar), 132.38 ($\underline{C}HCCl$), 148.14, 158.22, 165.12 (C-Ar); Anal. calcd for $C_{21}H_{26}ClN_3O_3$ (403.91): C, 62.45; H, 6.49; N, 10.40, found: C, 62.54; H, 6.36; N, 10.30; $[\alpha]_D^{20}=-122.2$ (*c* 0.09, $CHCl_3$).

Compound **63** was synthesized under the same reaction conditions, starting from ***ent*-5**; $[\alpha]_D^{20} = +114.6$ (*c* 0.19, $CHCl_3$).

4.53. (2*S*,4*R*)-*N*-[(2-(1-Benzyl-4-hydroxypyrrolidin-2-yl)ethyl]-5-chloro-2-methoxy-4-methylaminobenzamide 64

Compound **26** was synthesized from **24** (17.1 mg, 0.08 mmol) and was used as an amine precursor instead of **4** together with a suspension of 5-chloro-2-methoxy-4-(methylamino)benzoic acid (21.1 mg, 0.09 mmol), HOBt (13.1 mg, 0.09 mmol) and DCC (17.8 mg, 0.09 mmol) in EtOAc (10 mL) and reacted as described for ***ent*-63** to give **64** (9.0 mg, 27% over two reaction steps) as a red solid. Mp: 183–189°C. Purification was performed by flash chromatography (CH_2Cl_2/MeOH = 99:1) and HPLC (column: RP 18, eluent: MeOH/H_2O = 95:5). EI-MS $m/z = 399$ ($C_{22}H_{26}ClN_3O_2$); TLC: $R_f = 0.15$ (CH_2Cl_2/MeOH = 9:1); IR (film): *v* 3397, 2923, 2854, 1735, 1631, 1600, 1519, 1457, 1334, 1280, 1249, 1214, 1130, 1033, 971, 917, 809, 755, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 1.65–2.41 (m, 6H, H-3a/H-3b/H-5a/CH_2-CH_2-NH/CH_2-CH_2-NH), 2.50 (m, 1H, H-2), 2.89 (brd, 1H, $J = 10.6$ Hz, H-5b), 2.96 (brd, 3H, $J = 5.0$ Hz, NHCH_3), 3.18 (d, 1H, $J = 13.1$ Hz, NCH_2Ph), 3.56 (m, 2H, CH$_2$-CH_2-NH/CH$_2$-CH_2-NH), 3.90 (s, 3H, OCH_3), 4.09 (d, 1H, $J = 13.1$ Hz, NCH_2Ph), 4.16 (m, 1H, H-4), 4.71 (m, 1H, NHCH$_3$), 6.10 (s, 1H, CHCOCH$_3$), 7.19–7.37 (m, 5H, Ar), 7.80 (brs, 1H, NHCH$_2$), 8.12 (s, 1H, CHCCl); HR-EIMS: 399.17149 (Anal. calcd for $C_{22}H_{26}ClN_3O_2$: 399.17136), 198.03255 (Anal. calcd for $C_9H_9ClNO_2$: 198.03218), 176.10714 (Anal. calcd for $C_{11}H_{14}NO$: 176.10754), 112.07583 (Anal. calcd for $C_6H_{10}NO$: 112.07624), 198.03241 (Anal. calcd for $C_9H_9NO_2Cl$: 198.03218); $[\alpha]_D^{20} = +40.0$ (*c* 0.05, $CHCl_3$).

***ent*-64** could be synthesized under the same reaction conditions as described for **64**. Purification of ***ent*-64** by HPLC was not necessary.

4.54. (2*S*,4*R*)-*N*-[(2-(1-Benzyl-4-hydroxypyrrolidin-2-yl)ethyl]-5-chloro-2-methoxy-4-methylaminobenzamide *ent*-65

Compound **25** was synthesized from **21** (11.5 mg, 0.053 mmol) and used as an amine precursor instead of **4** to react with a suspension of 5-chloro-2-methoxy-4-(methylamino)benzoic acid (13.9 mg, 0.06 mmol), HOBt (8.7 mg, 0.06 mmol) and DCC (12.0 mg, 0.06 mmol) in EtOAc (15 mL) as described for ***ent*-63** to give ***ent*-65** (9.3 mg, 41%) as an opaque solid. Mp: 110°C. Purification was performed by flash chromatography (CH_2Cl_2/MeOH = 99:1) and HPLC (column: RP 18, eluent: MeOH/H_2O = 95:5). EI-MS $m/z = 417$ [M^+]; TLC: $R_f = 0.1$ (CH_2Cl_2/MeOH = 9:1); IR (film): *v* 3394, 2923, 2854, 1739, 1604, 1519, 1461, 1373, 1334, 1280, 1249, 1214, 1033, 809, 752, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 1.41–2.26 (m, 6H, H-3a/H-3b/H-5a/CH$_2$-CH$_2$-NH/CH$_2$-CH$_2$-NH), 2.88 (m, 1H, H-2), 2.96 (brd, 3H, $J = 5.0$ Hz, NHCH_3), 3.28 (m, 2H, NCH_2Ph/H-5b), 3.51 (m, 2H, CH$_2$-CH$_2$-NH/CH$_2$-CH$_2$-NH), 3.91 (s, 3H, OCH_3), 4.06 (d, 1H, $J = 13.5$ Hz, NCH_2Ph), 4.38 (m, 1H, H-4), 4.72 (m, 1H, NHCH$_3$), 6.11 (s, 1H, CHCOCH$_3$), 7.19–7.34 (m, 5H, Ar), 7.76 (brs, 1H, NHCH$_2$), 8.11 (s, 1H, CHCCl); HR-EIMS: 417.18210 (Anal. calcd for $C_{22}H_{28}ClN_3O_3$: 417.18192), 326.12712 (Anal. calcd for $C_{15}H_{21}ClN_3O_3$: 326.12714), 198.03241 (Anal. calcd for $C_9H_9ClNO_2$: 198.03218); $[\alpha]_D^{20} = -36.8$ (*c* 0.13, $CHCl_3$).

Compund **65** was synthesized under the same reaction conditions, starting from ***ent*-65**; $[\alpha]_D^{20} = +22.9$ (*c* 0.09, $CHCl_3$).

4.55. (2*R*,4*S*)-*N*-[(1-Benzyl-4-methylpyrrolidin-2-yl)-methyl]-5-chloro-2-methoxy-4-methylaminobenzamide 66

Compound **50** was synthesized from **48** (29.2 mg, 0.13 mmol) and used as an amine precursor to react with a suspension of 5-chloro-2-methoxy-4-(methylamino)-benzoic acid (34.89 mg, 0.16 mmol), HOBt (22.2 mg, 0.15 mmol) and DCC (30.67 mg, 0.15 mmol) in EtOAc (10 mL) as described for ***ent*-63** to give **66** (9.0 mg, 27% over two reaction steps) as a colorless, glutinous mass. Purification was performed by flash chromatography (CH_2Cl_2/MeOH = 99:1) and HPLC (column: RP 18, eluent: MeOH/H_2O = 95:5). EI-MS $m/z = 401$ [M^+]; TLC: $R_f = 0.34$ (CH_2Cl_2/MeOH = 9:1); IR (film): *v* 3370, 2927–2796, 1643, 1600, 1515, 1457, 1369, 1330, 1280, 1245, 1137, 1037, 917, 809, 748, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.94 (d, 3H, $J = 6.7$ Hz, CH_3), 1.55 (m, 1H, H-3a), 1.87 (m, 2H, H-3b/H-5a), 2.10 (m, 1H, H-4), 2.96 (m, 5H, H-5b/H-2/NHCH_3), 3.27 (d, 1H, $J = 12.8$ Hz, NCH_2Ph), 3.33 (ddd, 1H, $J = 13.8$, 3.9, 2.5 Hz, CH_2NH), 3.79 (ddd, 1H, $J = 13.8$, 7.7, 2.6 Hz, CH$_2$NH), 3.87 (s, 3H, OCH_3), 4.04 (d, 1H, $J = 13.0$ Hz, NCH$_2$Ph), 4.71 (m, 1H, NHCH$_3$), 6.12 (s, 1H, CHCOCH$_3$), 7.19–7.38 (m, 5H, Ar), 8.15 (s, 1H, CHCCl), 8.36 (m, 1H, NHCH$_2$); ^{13}C NMR ($CDCl_3$, 90.56 MHz): δ 18.53 (CH_3), 31.72 (C-4), 35.65 (NHCH_3), 37.04 (C-3), 41.39 (CH_2NH$_2$), 56.37 (OCH_3), 58.51 (NCH_2Ph), 61.98 (C-2), 62.23 (C-5), 112.35 (CHCOCH$_3$), 127.06, 128.26, 128.68 (C-Ar), 134.09 (CHCCl), 144.53, 156.80, 163.29 (C-Ar), 170.15 (CONH); HR-EIMS: 401.18726 (Anal. calcd for $C_{22}H_{28}ClN_3O_2$: 401.18701), 174.12785 (Anal. calcd for $C_{12}H_{16}N$: 174.12828); $[\alpha]_D^{20} = +69.5$ (*c* 0.14, $CHCl_3$).

***ent*-66** could be synthesized under the same reaction conditions as described for **66**; $[\alpha]_D^{20} = -70.0$ (*c* 0.2, $CHCl_3$).

4.56. (2*R*,4*S*)-*N*-[(1-Benzyl-4-butylpyrrolidin-2-yl)-methyl]-5-chloro-2-methoxy-4-methylaminobenzamide 67

Compound **51** (22.0 mg, 0.92 mmol) and a suspension of 5-chloro-2-methoxy-4-(methylamino)benzoic acid (21.69 mg, 0.10 mmol), HOBt (15.09 mg, 0.10 mmol) and DCC (21.16 mg, 0.10 mmol) in EtOAc (15 mL) was reacted and worked up (CH_2Cl_2/MeOH = 98:) as described for ***ent*-63** to give **67** (22.6 mg, 60%) as a yellowish, glutinous mass. TLC: $R_f = 0.3$ (CH_2Cl_2/

MeOH = 9:1); IR (film): ν 3367, 3062–2796, 1600, 1511, 1457, 1334, 1280, 1245, 1214, 1153, 1037, 809, 752, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.83 (t, 3H, $CH_2CH_2CH_2CH_3$), 1.22 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.55 (m, 1H, H-3a), 1.85 (m, 2H, H-3b/H-5a), 1.99 (m, 1H, H-4), 2.88 (m, 1H, H-2), 2.96 (d, 3H, J = 5.1 Hz, $NHCH_3$), 3.03 (dd, 1H, J = 8.2, 6.2 Hz, H-5b), 3.24 (d, 1H, J = 13.0 Hz, NCH_2Ph), 3.35 (ddd, 1H, J = 13.7, 3.8, 2.4 Hz, CH_2NH), 3.79 (ddd, 1H, J = 13.7, 7.6, 2.3 Hz, CH_2NH), 3.85 (s, 3H, OCH_3), 4.04 (d, 1H, J = 13.0 Hz, NCH_2Ph), 4.71 (m, 1H, $NHCH_3$), 6.13 (s, 1H, $CHCOCH_3$), 7.19–7.39 (m, 5H, Ar), 8.16 (s, 1H, CHCCl), 8.36 (brd, 1H, J = 3.8 Hz, $NHCH_2$); Anal. calcd for $C_{25}H_{34}ClN_3O_2$ (444.02): C, 67.63; H, 7.72; N, 9.46, found: C, 67.23; H, 7.75; N, 9.35; $[\alpha]_D^{20}$ = +89.5 (c 0.29, $CHCl_3$).

***ent*-67** could be synthesized under the same reaction conditions as described for **67**; $[\alpha]_D^{20}$ = −96.5 (c 0.45, $CHCl_3$).

4.57. (2*R*,4*S*)-*N*-[(2-Benzyl-4-methylpyrrolidin-2-yl)-ethyl)]-5-chloro-2-methoxy-4-methylaminobenzamide 68

Compound **58** was synthesized from **56** (11.7 mg, 0.055 mmol) and reacted with a suspension of 5-chloro-2-methoxy-4-methylaminobenzoic acid (14.37 mg, 0.07 mmol), HOBt (9.05 mg, 0.06 mmol) and DCC (12.36 mg, 0.06 mmol) in EtOAc (10 mL) and worked up (CH_2Cl_2/MeOH = 99:1) as described for ***ent*-63** to give **68** (8.0 mg, 35% over two reaction steps) as an orange, opaque solid. Mp: 118°C. EI-MS m/z = 415 [M^+]; TLC: R_f = 0.45 (CH_2Cl_2/MeOH = 9:1); IR (film): ν 3413, 2927–2792, 1724, 1639, 1604, 1519, 1457, 1330, 1280, 1245, 1214, 1130, 1037, 809, 752, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.96 (d, 3H, J = 6.4 Hz, CH_3), 1.88 (m, 7H, H-3a/H-3b/H-5a/CH_2-CH_2-NH-/CH_2-CH_2-NH-), 2.27 (m, 1H, H-4), 2.63 (m, 1H, H-2), 2.98 (m, 4H, H-5b/$NHCH_3$), 3.20 (d, 1H, J = 12.8 Hz, NCH_2Ph), 3.53 (m, 2H, CH_2-CH_2-NH-/CH_2-CH_2-NH-), 3.88 (s, 3H, OCH_3), 4.01 (d, 1H, J = 12.8 Hz, NCH_2Ph), 4.70 (m, 1H, $NHCH_3$), 6.10 (s, 1H, $CHCOCH_3$), 7.19–7.37 (m, 5H, Ar), 7.80 (brs, 1H, $NHCH_2$), 8.11 (s, 1H, CHCCl); HR-EIMS: 415.20226 (Anal. calcd for $C_{23}H_{30}ClN_3O_2$: 415.20267), 324.14785 (Anal. calcd for $C_{16}H_{23}ClN_3O_2$: 324.14789), 174.12863 (Anal. calcd for $C_{12}H_{16}N$: 174.12828), 110.09727 (Anal. calcd for $C_7H_{12}N$: 110.09698); $[\alpha]_D^{20}$ = +48.4 (c 0.15, $CHCl_3$).

***ent*-68** could be synthesized under the same reaction conditions as described for **68**; $[\alpha]_D^{20}$ = −56.5 (c 0.09, $CHCl_3$).

4.58. (2*R*,4*S*)-*N*-[(2-(1-Benzyl-4-butylpyrrolidin-2-yl)-ethyl)]-5-chloro-2-methoxy-4-methylaminobenzamide 69

Compound **59** was synthesized from **57** (10.5 mg, 0.04 mmol) and was reacted with a suspension of 5-chloro-2-methoxy-4-(methylamino)benzoic acid (10.6 mg, 0.05 mmol), HOBt (6.78 mg, 0.05 mmol) and DCC (9.29 mg, 0.05 mmol) in EtOAc (10 mL) and further worked up (CH_2Cl_2/MeOH = 99:1) as described for ***ent*-63** to give **69** (6.9 mg, 37% over two reaction steps) as a colorless, opaque solid. Mp: 78°C; EI-MS m/z = 457 [M^+]; TLC: R_f = 0.36 (CH_2Cl_2/MeOH = 9:1); IR (film): ν 3409, 3062–2792, 1639, 1604, 1519, 1457, 1330, 1280, 1245, 1214, 1153, 1130, 1037, 917, 809, 752, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz): δ 0.85 (t, 3H, $CH_2CH_2CH_2CH_3$), 1.25 (m, 6H, $CH_2CH_2CH_2CH_3$), 1.53–2.15 (m, 7H, H-3a/H-3b/H-4/H-5a/CH_2-CH_2-NH/CH_2-CH_2-NH), 2.60 (m, 1H, H-2), 3.00 (m, 4H, $NHCH_3$/H-5b), 3.18 (d, 1H, J = 12.1 Hz, NCH_2Ph), 3.53 (m, 2H, CH_2-CH_2-NH/CH_2-CH_2-NH), 3.89 (s, 3H, OCH_3), 4.02 (d, 1H, J = 12.1 Hz, NCH_2Ph), 4.71 (m, 1H, $NHCH_3$), 6.10 (s, 1H, $CHCOCH_3$), 7.17–7.39 (m, 5H, Ar), 7.80 (brs, 1H, $NHCH_2$), 8.11 (s, 1H, CHCCl); HR-EIMS: 457.24973 (Anal. calcd for $C_{26}H_{36}ClN_3O_2$: 457.24960), 366.19450 (Anal. calcd for $C_{19}H_{29}ClN_3O_2$: 366.19482), 216.17526 (Anal. calcd for $C_{15}H_{22}N$: 216.17523), 152.14337 (Anal. calcd for $C_{10}H_{18}N$: 152.14392); $[\alpha]_D^{20}$ = +67.8 (c 0.2, $CHCl_3$).

***ent*-69** could be synthesized under the same reaction conditions as described for **69**; $[\alpha]_D^{20}$ = −55.7 (c 0.31, $CHCl_3$).

4.59. Dopamine receptor binding studies

Receptor binding studies were carried out as described in the literature.[46] In brief, the dopamine D1 receptor assay was done with bovine striatal membranes at a final protein concentration of 45 μg/assay tube and the radioligand [^{3}H]SCH 23390 at 0.3 nM (K_d = 0.35–0.75 nM).

Competition experiments with the human $D2_{long}$, $D2_{short}$, D3 and D4.4 receptors were run with preparations of membranes from CHO cells expressing the corresponding receptor and [^{3}H]spiperone at a final concentration of 0.1 nM. The assays were carried out at a protein concentration of 5–25 μg/assay tube and K_d values of 0.10 nM for $D2_{long}$ and $D2_{short}$, 0.10–0.40 nM for D3 and 0.10–0.45 nM for D4.4.

Protein concentration was established by the method of Lowry using bovine serum albumin as standard.[48]

4.60. 5-HT receptor binding studies

Receptor binding experiments were done with cortical homogenates prepared from porcine brain which was obtained from the local slaughterhouse. The cortex material was dissected and frozen at −80°C. Membranes were prepared by thawing, cutting up and homogenizing in an aqueous solution of sucrose (0.1 M). The suspension was washed by centrifugation at 2,500 g. The resulting supernatant was then pelleted by centrifugation at 80,000 g for 40 min. The pellet was resuspended in Tris–EDTA buffer (50 mM Tris–HCl, 1 mM EDTA; pH 7.4), homogenized with a Potter–Elvehjam homogenizer and stored at −80°C in small aliquots.

For 5-HT1$_A$ receptor binding assay porcine cortical membranes were diluted with binding buffer (50 mM Tris–HCl, 4 mM $CaCl_2$, 0.1% ascorbic acid and 10 nM pargyline; pH 7.4) to a final concentration of 460 μg protein/assay tube (K_d values from 2.4–4.8 nM). Tubes were prepared with the radioligand [^{3}H]8-OH-DPAT (0.5 nM) (specific activity 135.0 Ci/mmol; PerkinElmer) and varying concentrations of test compounds (from 0.01–10,000 nM). Nonspecific binding was determined in the presence of serotonine (10 μM). Incubation was started by adding membranes to the assay tube with a final volume of 800 μL, was continued for 60 min at 37°C and stopped by rapid filtration through GF/B filters precoated with 0.3% polyethylenimine, using an automated cell harvester (Inotech, CH). Filters were washed five times with ice-cold Tris–EDTA buffer, dried and counted in a MicroBeta Trilux (PerkinElmerWallac).

Binding assay with 5-HT2 receptors was done at 200 μg protein/assay tube with the radioligand [^{3}H]ketanserine (specific activity 63.3 Ci/mmol; PerkinElmer) at K_d values from 2.6–3.1 nM and methysergide (10 μM) for determination of nonspecific binding. Incubation was carried out at a final volume of 500 μL for 60 min at 37°C and worked up as described above.

4.61. Data analysis

The resulting competition curves were analyzed by nonlinear regression using the algorithms in PRISM (GraphPad Software, San Diego, CA). The data was initially fitted using a sigmoid model to provide an IC_{50} value, representing the concentration corresponding to 50% of maximal inhibition. The IC_{50} values were transformed to K_i values according to the equation of Cheng and Prusoff.[49]

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