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Syntheses of New Chiral 1,2-Diamines and δ-Amino-Alcohols and their Application in Catalytic Enantioselective C-C Bond Formations at an Elevated Temperature of up to 110 °C[1]

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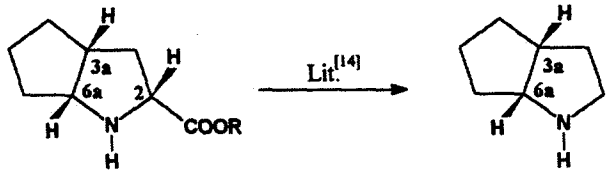
Abstract: The syntheses of new chiral 1,2-diamines **6a-e** and chiral δ-amino alcohols (–)-**10a-e**, (+)-**10d-e** and their use as ligands in catalytic asymmetric additions of diethylzinc to benzaldehyde are described. The diamines were found to be efficient catalysts which gave the corresponding alcohol in good to high ee's (e.g. 88% ee for Li-**6a**) at a reaction temperature of 110 °C. Also the δ-amino alcohols, particularly (–)- and (+)-**10e**, gave (*S*)- and (*R*)-1-phenyl-1-propanol in high enantiomeric excesses (up to 91% ee) under mild reaction conditions.

One of the most challenging subjects in organic synthesis during this decade are catalytic methods for asymmetric reactions[2]. Especially amino acid-based chiral auxiliaries are often used as effective catalysts in stereoselective synthesis[3]. Since *Oguni* and *Omi*[4] firstly reported on the use of catalytic amounts of optically active β-amino alcohols in such reactions numerous other chiral ligands have been developed, e.g. piperazines[5], pyridines[6], γ-amino alcohols[7] and 1,2-diols[8].



(2*R*,3a*R*,6a*R*)-**1a** (R=H)
(2*R*,3a*R*,6a*R*)-**1b** (R=CH_2Ph)

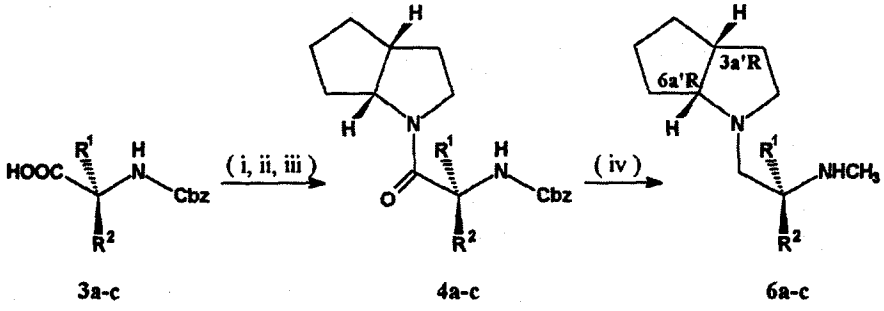
(*all-R*)-**2**

These reports prompted us to prepare new chiral auxiliaries from the non-proteinogenic, structurally rigid amino acid (2*R*,3a*R*,6a*R*)-octahydrocyclopenta[b]pyrrole-2-carboxylic acid (2*R*,3a*R*,6a*R*)-**1a** and the corresponding amine (3a*R*,6a*R*)-**2**.

The unnatural amino acid (*all-S*)-**1a** is an intermediate in the industrial production of the highly potent angiotensin converting enzyme (ACE) inhibitor Ramipril[9]. Its enantiomer (*all-R*)-**1a** is a waste product derived from the resolution of the racemic benzyl ester derivative (2*RS*,3a*RS*,6a*RS*)-**1b** via diastereomeric salts.

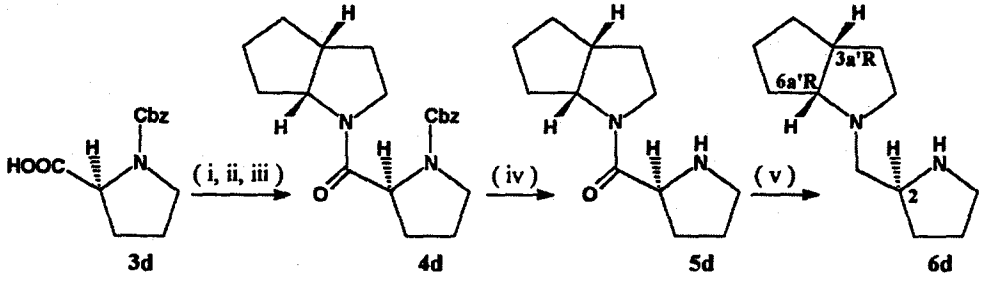
Because the ester hydrochloride (*all-R*)-**1b**-HCl could not be converted in the racemic (2*RS*,3a*RS*,6a*RS*)-**1b** it has no further use in the route to Ramipril. Thus, it is one of our goals to find new applications for the waste material (*all-R*)-**1b**. The present paper deals with the synthesis of novel chiral 1,2-diamines and δ-amino alcohols and their use as auxiliaries in asymmetric catalysis.

The 1,2-diamines **6a-c** are prepared in three steps according to scheme 1. The *N*-benzyloxycarbonyl protected amino acids **3a-c** are treated with the amine (*all-R*)-**2** using the mixed anhydride coupling method to give the dipeptides **4a-c**. After reduction of the dipeptides with an excess of $LiAlH_4$ in refluxing THF the *N*-methyl-1,2-diamines **6a-c** are obtained in 41% to 56% overall yield.

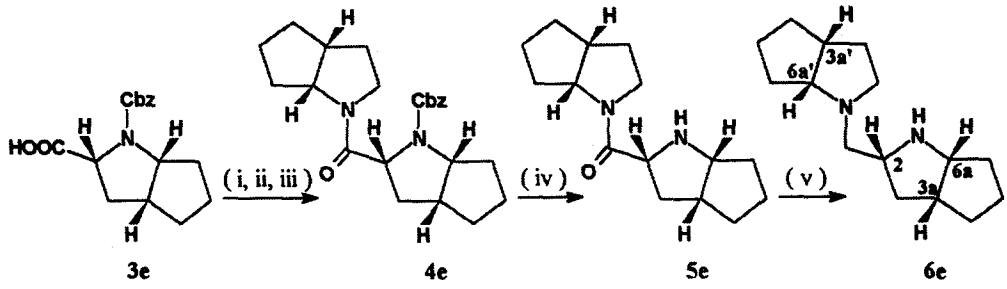


Scheme 1: Synthesis of diamines **6a-c**: (i): *N*-methylmorpholine, (ii): ethyl chloroformate, (iii): amine *(all-R)*-**2**, (iv): $LiAlH_4$ / THF, (Cbz = CO_2CH_2Ph; **a**: R^1 = H, R^2 = CH_2Ph; **b**: R^1 = Ph, R^2 = H; **c**: R^1 = 1,4-cyclohexadien-1-yl, R^2 = H)

The synthesis of the diamines **6d** (scheme 2) and **6e** (scheme 3) from Cbz-protected (*S*)-proline **3d** respectively (*all-R*)-**3e** is mostly identical to the route mentioned above except the removal of the protecting group from the intermediates **4d** and **4e**. Deblocking of the amino group was carried out by catalytic transfer hydrogenation with 10% Pd/C as catalyst and cyclohexene as hydrogen donor in refluxing methanol. After filtration and removal of the solvent the amides **5d** and **5e** are obtained mostly quantitative in high purity. Reduction of the amides with $LiAlH_4$ in refluxing THF for 18 h afforded the 1,2-diamines **6d** and **6e**.

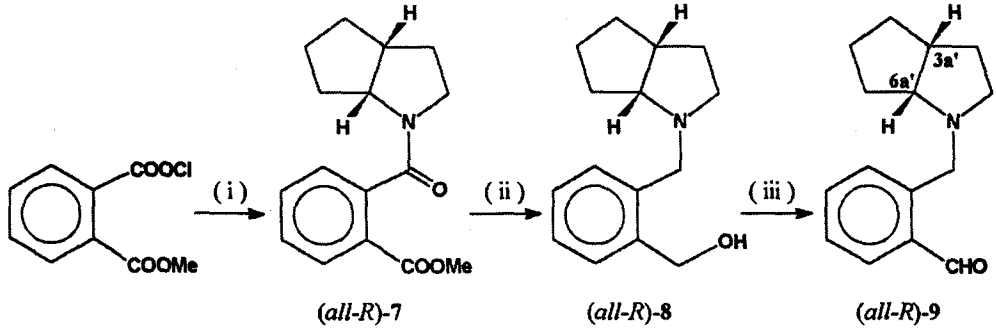


Scheme 2: Synthesis of diamine **6d**: (Cbz = CO_2CH_2Ph), (i): *N*-methyl-morpholine, (ii): ethyl chloroformate, (iii): amine *(all-R)*-**2**, (iv): cyclohexene, Pd/C, (v): $LiAlH_4$/THF



Scheme 3: Synthesis of diamine **6e:** (Cbz = CO_2CH_2Ph), (i): *N*-methyl-morpholine, (ii): ethyl chloroformate, (iii): amine *(all-R)*-**2**, (iv): cyclohexene, Pd/C, (v): $LiAlH_4$/THF

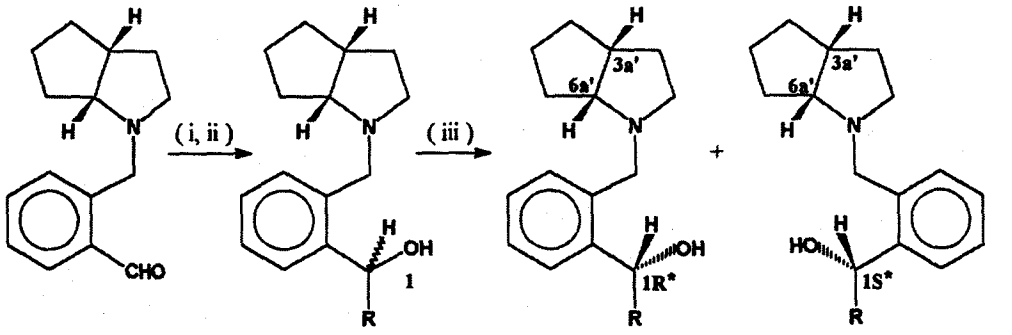
The chiral δ-amino alcohols (–)-**10a-e** and (+)-**10d-e** are synthesized in 4 steps as shown in scheme 4 and 5. The acid chloride of phthalic acid monomethylester is coupled with the amine (*all-R*)-**2** to give the amido ester (*all-R*)-**7** in 96 % yield. After the following reduction with an eightfold molar excess of lithium aluminium hydride the amino alcohol (*all-R*)-**8** is obtained in 69 % yield. Swern oxidation of the alcohol (*all-R*)-**8** leads to the γ-amino aldehyde (*all-R*)-**9** in 88 % yield.



Scheme 4: Synthesis of γ-aminoaldehyd **9**: (i): amine (*all-R*)-**2**, (ii): $LiAlH_4$ / THF, (iii): $(COCl)_2$, DMSO, NEt_3

The last step is the diastereoselective addition of alkyl- or aryl-*Grignard* reagents to the amino aldehyde (*all-R*)-**9** to give the desired δ-amino alcohols **10a-e** with moderate diastereoselectivities between 51:49 and 59:41 [(–)-diastereomer: (+)-diastereomer]. The separation of diastereomers is achieved by flash chromatography. In all cases the major (–)-diastereomer could be separated, while the minor diastereomers with positive specific rotations were currently only obtained in the cases of **10d** and **10e**. However the absolute configuration at C1 has not been determined yet.

Enantioselective additions of diethylzinc to benzaldehyde in the presence of various catalytic amounts of the diamine **6a** were carried out at different temperatures. The data obtained are shown in table 1.



(*all-R*)-9 (*1RS,3a'R,6a'R*)-**10a-e** (–)-(1*R**,3a'*R*,6a'*R*)-**10a-e** (+)-(1*S**,3a'*R*,6a'*R*)-**10d-e**

Scheme 5: Synthesis of the δ-amino alkohols (–)-(1*R**,3a'*R*,6a'*R*)-**10a-e** and (+)-(1*S**,3a'*R*,6a'*R*)-**10d-e**[10]: (i): RMgX, (ii): hydrolysis, (iii): flash chromatography, (**a**: R = methyl, **b**: R = ethyl; **c**: R = benzyl; **d**: R = α-naphthyl; **e**: R = *o*-tolyl)

Table 1: Enantioselective addition of diethylzinc to benzaldehyde; variation of the reaction temperature and the concentration of the catalyst **6a**, product: (*R*)-1-phenyl-1-propanol

Entry	cat*: **6a** [mol %][a]	temp. [°C]	chem. yield [%]	$[\alpha]_D^{20}$ *(c)*[b]	e.e. [%][c]
1	10	–30[d]	70	+3.9 (4.62)	9
2	10	0[e]	76	+11.03 (4.78)	24
3	10	22	70	+12.8 (4.69)	28
4	10	40	70	+14.5 (4.74)	32
5	10	60	68	+17.9 (4.45)	39
6	10	80	71	+23.1 (4.56)	51
7	10	100	55	+31.4 (4.85)	69
8	10	110	70	+33.1 (4.95)	73
9	2.5	110	55	+14.8 (5.03)	33
10	10	110	70	+33.1 (4.95)	73
11	25	110	60	+39.3 (5.49)	87
12	40	110	57	+34.2 (4.72)	75

a) mol% chiral catalyst relative to benzaldehyde, b) measured in chloroform, c) referred to $[\alpha]_D^{20} = +45.45$ (*c*=5.15, $CHCl_3$) for *(R)*-1-phenyl-1-propanol, d) 8h at – 30 °C, then 30h at r.t., e) 5.5h at 0 °C, then 35h at r.t.

Enantiomeric excesses of the obtained 1-phenyl-1-propanols were determined by comparision of the specific rotations with the literally known specific rotations of the pure alcohol. The enantioselectivity ranges from low (entry 1) to high (entry 11) depending on the reaction conditions. It is known from the literature that optimum reaction temperatures for the enantioselective addition of diethylzinc to aldehydes are between room temperature and -30 °C. The diamines show an opposite behaviour. Only a few examples are known which

show the same ability[11]. The highest enantioselectivity for diamine **6a** with an enantiomeric excess of 87 % (entry 11) is obtained for a reaction temperature of 110 °C and a concentration of 25 mol% of the ligand **6a**. Therefore we tested the diamines **6b-e** respectively their corresponding lithiated counterparts in the enantioselective diethylzinc addition to benzaldehyde at a reaction temperature of 110 °C (table 2). The best results are obtained with the diamine **6a** and its lithiated salts (entries 13-15). A concentration of 25 mol% leads to 1-phenyl-1-propanol in an enantiomeric excess of 88 %. Table 2 also shows the possibility that lithiated ligands could be the more enantioselective catalysts then the parent compounds like some authors already reported[12].

Table 2: Enantioselective ethylation of benzaldehyde, catalysts: **6a-e** reaction temperature: 110 °C, product: 1-phenyl-1-propanol

Entry	cat.*	conc. [mol %][a]	chem. yield. [%]	$[\alpha]_D^{20}$ (*c*)[b]	e.e. [%][c]	config.
13	**6a**	10	70	+33.1 (4.95)	73	*R*
14	Li-**6a**	10	68	+35.1 (5.32)	78	*R*
15	Li-**6a**	25	55	+44.0 (4.92)	88	*R*
16	Li-**6a**	10[e]	62	+14.6 (5.36)	32	*R*
17	Li-**6a**	25[e]	53	+17.9 (5.26)	43	*R*
18	**6b**	10	56	−14.2 (5.49)	31	*S*
19	Li-**6b**	10	69	−29.1 (5.46)	64	*S*
20	**6c**	10	54	−9.6 (5.78)	21	*S*
21	Li-**6c**	10	61	−25.2 (5.48)	56	*S*
22	**6d**	10	52	−15.3 (5.43)	34	*S*
23	Li-**6d**	10	32	−20.3 (5.61)	45	*S*
24	**6e**	10	9[d]	+3.8 (4.93)	8	*R*
25	Li-**6e**	10	45	+16.6 (5.34)	37	*R*

a) mol% chiral catalyst relative to benzaldehyde, b) measured in chloroform, c) referred to $[\alpha]_D^{20} = +45.45$ (*c*=5.15, $CHCl_3$) for *(R)*-1-phenyl-1-propanol, d) catalyst is unstable under the reaction conditions, e) reaction temperature: 25 °C.

Using the *δ*-amino alcohols (−)-**10a-e** and (+)-**10d-e**, the reaction of benzaldehyde with diethylzinc was performed at room temperature. High enantiomeric excesses around 90 % were obtained in case of the sterically constrained amino alcohols (+)-**10d**, (−)-**10e** and (+)-**10e** containing the bulky *α*-naphthyl- or *o*-tolyl groups at position 1. Especially both diastereomers of the *o*-tolyl-amino alcohol **10e** (entries 31-32) lead to high enantiomeric excesses. When using the (−)-diastereomer as chiral ligand the (*S*)-alcohol is obtained and vice versa. The conclusion of this fact is that the stereochemical control of the reaction is defined by the configuration of the C1 atom of the *δ*-amino alcohol. The lithiated ligand Li-(−)-**10e** (entry 33) leads to a decrease of enantioselectivity unlike the increasing observed for the 1,2-diamines.

Table 3: Enantioselective ethylation of benzaldehyde at room temperature and a catalyst concentration of 10 mol%[a], catalysts: (–)-**10a-e**, (+)-**10d-e**, product: 1-phenyl-1-propanol

Entry	cat.*	chem. yield. [%]	$[\alpha]_D^{20}$ (*c*)[b]	e.e. [%][c]	configuration
26	(–)-**10a**	78	+22.5	50	*R*
27	(–)-**10b**	73	+36.1	79	*R*
28	(–)-**10c**	70	+21.7	48	*R*
29	(–)-**10d**	71	-28.4	62	*S*
30	(+)-**10d**	68	+41.3	91	*R*
31	(–)-**10e**	76	–40.9	90	*S*
32	(+)-**10e**	75	+40.5	89	*R*
33	Li-(–)-**10e**	78	–37.5	82	*S*

a) mol% chiral catalyst relative to benzaldehyde, b) measured in chloroform (c=5.15), c) referred to $[\alpha]_D^{20} = +45.45$ (*c*=5.15, $CHCl_3$) for *(R)*-1-phenyl-1-propanol

Acknowledgment: We are indebted to Degussa AG, Hoechst AG, Witco GmbH, DSM Andeno GmbH and the Fonds der Chemischen Industrie for providing us with chemicals and for the financial support.

Experimental Section

Melting points were taken on a melting point apparatus according to Dr. Linström and are uncorrected. Specific rotations were measured on a Perkin-Elmer automatic polarimeter. IR spectra were recorded on a Philips PU 9706 spectrophotometer. The ^{1}H-NMR and ^{13}C-NMR spectra were registrated on a Bruker AM 300 spectrometer using TMS as internal standard. Mass spectra were recorded on a Finnigan-MAT 212 (data system 300; CI, *i*-butane). Elemental analyses (C, H, N) were performed on a Carlo Erba Stumentalione (MOD 1104) analyzer. Column chromatography was performed using Merck silica gel 60 (40-63 μm, pH= 7.0 ± 0.5). Solvents for chromatography were used without further purification. Analytical TLC was performed on Merck precoated Kieselgel 60 F-254 plates. Detections were made using either I_2 or UV light. The length of the column was 53 cm and its diameter was 3 cm. Commercially available chemicals were used without further purification. The purities of 1-phenyl-1-propanols were determined by NMR technique and by comparison of the measured index of refraction with literally known values. Phthalic acid monomethyl ester[13] and (*all-R*)-octahydrocyclopenta[b]pyrrole[14] were prepared according to the referred literature.

Cbz-protected amides: (1*S*,3a'*R*,6a'*R*)-**4a**, (1*R*,3a'*R*,6a'*R*)-**4b**, (1*R*,3a'*R*,6a'*R*)-**4c**, (2*S*,3a'*R*,6a'*R*)-**4d**, (3a'*R*,6a'*R*,2*R*,3a*R*,6a*R*)-**4e**; **General Procedure I**:

Under vigorous stirring and at – 25 °C, *N*-methylmorpholine (8.11 g, 80 mmol) in EtOAc (30 mL) and ethylchloroformate (8.64 g, 80 mmol) in EtOAc (30 mL) and after 20 min (3a*R*,6a*R*)-octahydrocyclopenta[b]pyrrole (3a*R*,6a*R*)-**2** (8.95 g, 80 mmol) was added to the Cbz-protected amino acids **3a-3e** (80 mmol) in EtOAc (250 mL). The resulting reaction mixtures are stirred at – 25 °C for 2 h, then 16 h at room temperature. The mixture is treated with H_2O (100 mL) and EtOAc (100 mL). The organic and aqueous layers

are separated and the aqueous layer extracted with EtOAc (2x 50 mL). The combined organic phases are successively washed with 10 % aq $NaHCO_3$ (3x 80 mL), sat. aq NaCl (80 mL), 2 N aq HCl (3x 80 mL) and sat. aq. NaCl (80 mL) in that order and dried ($MgSO_4$). The solvent is evaporated under reduced pressure and the crude products purified by crystallization or shortpath distillation.

(1*S*,3a'*R*,6a'*R*)-[2-Amino-(*N*-benzyloxycarbonyl)-1-(hexahydro-cyclopenta-[b]pyrrole-1'-yl)-3-phenyl]-propan-1-one (1*S*,3a'*R*,6a'*R*)-4a: work-up: crystallization with small amounts of diethyl ether at 4 °C; starting material: 29.9 g (100 mmol) cbz-protected (*S*)-phenylalanine **3a**; yield: 24.7 g (63 %); m.p.: 76-84 °C; $[\alpha]_D^{20}$ = – 51.5 (*c* = 1.25, $CHCl_3$); IR (KBr): ν = 3380 cm^{-1} (NH), 1615 (C=O), 1540 (NH); ^{1}H-NMR ($CDCl_3$): δ = 1.34–1.91 (m, 7H, H3a', 2x H4', 2x H5', 2x H6'), 2.2-2.34 (m, 0.36H, 0.36x H3'), 2.4-2.57 (m, 0.64H, 0.64x H3'), 2.57-2.71 (m, 0.85H, 0.85x H3'), 2.9-3.1 (m, 2.15H, 0.15x H3', 2x H2'), 3.17-3.4 (m, 1H, 1x C$\underline{H}_2$Ph), 3.47-3.7 (m, 1H, 1x C$\underline{H}_2$Ph), 4.03-4.17 (m, 1H, H6a'), 4.17-4.28 (m, 1H, 1x N$\underline{H}$CO), 4.64-4.83 (m, 1H, H1), 5.0-5.17 (m, 2H, OCOC$\underline{H}_2$Ph), 7.09-7.4 (m, 10H, aromatic H); ^{13}C-NMR ($CDCl_3$): δ (major rotamer) = 25.04, 29.26, 31.64, 34.95, 39.84 (C3', C4', C5', C6', $\underline{C}H_2$Ph), 41.24 (C3a'), 46.73 (C6a'), 53.67 (C2'), 63.12 (C1), 66.52 (O$\underline{C}H_2$Ph), 127.83, 128.21, 129.45 (aromatic C), 136.13 (q. aromatic C), 155.8 ($\underline{C}O_2CH_2Ph$), 169.1 (CON); δ (minor rotamer) = 25.39, 30.89, 33.01, 34.95, 40.41 (C3', C4', C5', C6', $\underline{C}H_2$Ph), 43.33 (C3a'), 45.37 (C6a'), 53.67 (C2'), 62.19 (C1), 66.52 (O$\underline{C}H_2$Ph), 126.74, 128.28, 129.22 (aromatic C), 136.13 (q. aromatic C), 155.8 ($\underline{C}O_2CH_2Ph$), 169.8 (CON); MS (CI, *i*-butane): 394 (MH^+, 100 %), 91 ($PhCH_2$, 5 %); Anal. calc. for $C_{24}H_{28}N_2O_3$ (392.5): C, 73.44; H, 7.19; N, 7.14; found: C, 73.55; H, 7.21; N, 6.91.

(1*R*,3a'*R*,6a'*R*)-[2-Amino-(*N*-benzyloxycarbonyl)-1-(hexahydro-cyclopenta-[b]pyrrole-1'-yl)-2-phenyl]-ethanone (1*R*,3a'*R*,6a'*R*)-4b: starting material: 16.9 g (59.3 mmol) cbz-protected (*R*)-phenylglycine **3b**; yield: 19.68 g (87.8%); $[\alpha]_D^{20}$ = – 218.3 (*c* = 0.45, $CHCl_3$); IR (NaCl): ν = 3400-3380 cm^{-1} (NH), 1615 (C=O), 1540 (NH); ^{1}H-NMR ($CDCl_3$): δ = 1.25–1.86 (m, 7H, H3a', 2x H4', 2x H5', 2x H6'), 1.86-2.11 (m, 1H, 1x H3'), 2.44-2.67 (m, 1H, 1x H3'), 3.14-3.56, 3.86-4.0 (4m, 2H, 2x H2'), 4.0-4.2, 4.2-4.31 (2m, 1H, H6a'), 4.94-5.14 (m, 2H, OCOC$\underline{H}_2$Ph), 5.36-5.43 (d, *J* = 9.32 Hz, 0.8H, 0.8x H1), 5.6-5.66 (d, *J* = 9.3 Hz, 0.2H, 0.2x H1), 6.27-6.34 (d, *J* = 9.3 Hz, 0.2 H, 0.2x N$\underline{H}CO_2$Ph), 6.4-6.49 (d, *J* = 9.38 , 0.8H, 0.8x N$\underline{H}CO_2$Ph), 7.11-7.4 (m, 10H, aromatic H); ^{13}C-NMR ($CDCl_3$): δ (major rotamer) = 25.09, 30.67, 31.45, 32.29 (C3', C4', C5', C6'), 41.42 (C3a'), 46.29 (C2'), 56.96 (C6a'), 63.52 (C1), 66.53 (O$\underline{C}H_2$Ph), 127.76, 128.08, 128.74 (aromatic C), 137.28 (q. aromatic C), 155.29 ($\underline{C}O_2CH_2Ph$), 167.19 (CON); δ (minor rotamer) = 25.20, 29.33, 31.85, 34.13 (C3', C4', C5', C6'), 43.79 (C3a'), 45.58 (C2'), 55.94 (C6a'), 62.78 (C1), 66.53 (O$\underline{C}H_2$Ph), 127.02, 128.22, 128.55 (aromatic C), 136.23 (q. aromatic C), 155.29 ($\underline{C}O_2CH_2Ph$), 167.19 (CON); MS (CI, *i*-butane): 379 (MH^+, 100 %), 91 ($PhCH_2$, 21 %), 335 ($MH^+ - CO_2$, 6 %); Anal. calc. for $C_{23}H_{26}N_2O_3$ (378.5): C, 72.9; H, 6.92; N, 7.40; found: C, 72.90; H, 6.85; N, 7.18.

(1*R*,3a'*R*,6a'*R*)-[2-Amino-(*N*-benzyloxycarbonyl)-2-cyclohexa-1'',4''-dienyl-1-(hexahydro-cyclopenta[b]pyrrole-1'-yl)]-ethanone (1*R*,3a'*R*,6a'*R*)-4c: starting material: 17.11 g (60 mmol) cbz-protected (*R*)-3,6-dihydrophenylglycine **3c**; yield: 19.32 g (84.7%); $[\alpha]_D^{20}$ = – 141.3 (*c* = 1.67, $CHCl_3$); IR (NaCl): ν = 3400-3380 cm^{-1} (NH), 1630 (C=O), 1540 (NH); ^{1}H-NMR ($CDCl_3$): δ = 1.24–2.0 (m, 7H, H3a', 2x H4', 2x H5', 2x H6'), 2.5-2.8 (m, 5.46H, 2x H3'', 2x H6'', 0.46x H3'), 3.24-3.37 (m, 0.54H, 0.54x H3'), 3.37-3.6 (m, 2H, 2x H2'), 3.86-3.96, 4.04-4.2, 4.2-4.4, 4.76-4.87, 4.96-5.16 (5m, 4H, H6a', NHCO, C$\underline{H}_2$Ph), 5.6-5.84 (m, 3H, olefinic H), 5.95-6.0, 6.0-6.11 (2m, 1H, H1), 7.2-7.36 (m, 5H, aromatic H); ^{13}C-NMR ($CDCl_3$): δ = major rotamer: 25.32, 26.52, 29.36, 30.87, 31.48, 33.33 (C3', C4', C5', C6', C3'', C6''), 41.51 (C3a'), 46.3 (C2'), 58.54 (C6a'), 63.36 (C1), 66.51 (O$\underline{C}H_2$Ph), 123.21-136.32 (aromatic and olefinic C), 155.55

($\underline{C}O_2CH_2Ph$), 166.77 (CON), minor rotamer: 25.12, 25.99, 29.36, 30.87, 31.48, 34.2 (C3', C4', C5', C6', C3", C6"), 43.78 (C3a'), 45.49 (C2'), 57.38 (C6a'), 62.83 (C1), 66.51 ($O\underline{C}H_2Ph$), 123.21-136.32 (aromatic and olefinic C), 155.55 ($\underline{C}O_2CH_2Ph$), 166.77 (CON); MS (CI, *i*-butane): 381 (MH^+, 100 %), 91 ($PhCH_2$, 31 %); Anal. calc. for $C_{23}H_{28}N_2O_3$ (380.5): C, 72.61; H, 7.42; N, 7.36; found: C, 72.54; H, 7.18; N, 7.05.

(2*S*,3a'*R*,6a'*R*)-(Hexahydro-cyclopenta[b]pyrrole-1'-yl)-[(*N*-benzyloxy–carbonyl)-pyrrolidin-2-yl]-methanone (2*S*,3a'*R*,6a'*R*)-4d: starting material: 14.95 g (60 mmol) cbz-protected (*S*)-proline **3d**; yield: 14.17 g (69 %); $[\alpha]_D^{20} = -87.2$ (c = 4.50, $CHCl_3$); IR (NaCl): ν = 1680-1620 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ = 1.04–1.94 (m, 11H, H3a', 2x H4', 2x H5', 2x H6', 2x H3, 2x H4), 1.94-2.2 (m, 1.44H, 1.44x H3'), 2.49-2.64 (m, 0.56H, 0.56x H3'), 3.08-3.12 (m, 4H, 2x H2', 2x H5), 3.94-4.2 (m, 2H, $OCO\underline{C}H_2Ph$), 4.29-4.6 (m, 1H, H6a'), 4.9-5.12 (m, 1H, H2), 7.11-7.33 (m, 5H, aromatic H); ^{13}C-NMR ($CDCl_3$): δ = rotational isomeres: 14.55 (C2), 20.26-34.74 (C3', C4', C5', C6', C3, C4), 41.11, 43.96 (C3a'), 45.47, 46.23, 47.09 (C2'), 58.04, 61.69, 62.86 (C6a'), 60.38 (C5), 66.51, 66.77, 67.04 ($O\underline{C}H_2Ph$), 127.42-128.43 (aromatic C), 136.22, 136.43 (q. aromatic C), 153.93, 154.67 ($\underline{C}O_2CH_2Ph$), 169.99-170.38 (CON); MS (CI, *i*-Butan): 343 (MH^+, 100 %); Anal. calc. for $C_{20}H_{26}N_2O_3$ (342.43): C, 70.15; H, 7.65; N, 8.18; found: C, 70.04; H, 7.33; N, 7.89.

(3a'*R*,6a'*R*,2*R*,3a*R*,6a*R*)-(Hexahydro-cyclopenta[b]pyrrole-1'-yl)-[(N-benzyl–oxycarbonyl)-octahydro-cyclopenta[b]pyrrole-2-yl]-methanone (3a'*R*,6a'*R*,2*R*,3a*R*,6a*R*)-4e: starting material: 12.26 g (42.27 mmol) cbz-protected (2*R*,3a*R*,6a*R*)-octahydro-cyclopenta[b]pyrrole-2-carboxylic acid **3e**; yield: 9.45 g (58.4 %); m.p.: 104-107 °C; $[\alpha]_D^{20} = -95.5$ (c = 1.11, $CHCl_3$); IR (NaCl): ν = 1670-1580 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ = 1.0–2.16 (m, 14H, 1x H3a', 2x H4', 2x H5', 2x H6', 1x H3a, 2x H4, 2x H5, 2x H6), 2.16-2.4 (m, 0.7H, 0.7x H3'), 2.4-2.8 (m, 1.3H, 1.3x H3'), 3.11-3.64, 3.71-3.83 (2m, 3H, 2x H3, 1x H2'), 3.83-3.94, 4.0-4.34 (2m, 2H, 1x H2', 1x H2), 4.34-4.6, 4.86-5.14 (2m, 4H, H6a', H6a, 2x $OC\underline{H}_2Ph$), 7.14-7.40 (m, 5H, aromatic H); ^{13}C-NMR ($CDCl_3$): δ = rotational isomeres: 24.22-37.04 (C3', C4', C5', C6', C3, C4, C5, C6), 41.49-44.26 (C3a', C3a), 45.94, 46.09 (C2'), 59.47-65.28 (C6a', C6a, C2), 66.66, 66.84, 67.22 ($O\underline{C}H_2Ph$), 127.09-128.21 (aromatic C), 136.09, 136.51, 136.66 (q. aromatic C), 153.78, 154.21, 154.47 ($O\underline{C}OCH_2Ph$), 169.84, 170.01, 171.02 (CON); MS (CI, *i*-butane): 384 (MH^+, 100 %), 249 ($MH^+ - CO_2CH_2Ph$, 4 %), 110 ($C_7H_{12}N$, 3 %); Anal. calc. for $C_{23}H_{30}N_2O_3$ (382.5): C, 72.22; H, 7.91; N, 7.32; found: C, 72.10; H, 8.15; N, 7.20.

***N*-Benzyloxycarbonyl-amides: (2*S*,3a'*R*,6a'*R*)-5d, (3a'*R*,6a'*R*,2*R*,3a*R*,6a*R*)-5e; General procedure II:**

The protected amino acid **4d,e** (50 mmol) is suspended in dry MeOH (50 mL) with 10 % Pd on active charcoal (4 g) and cyclohexene (70 mL). The reaction mixtures is refluxed for 4 h under argon. The reaction mixture is then filtered and all the volatile products and solvents are removed *in vacuo*. The resulting free 2-amino-carboxylic amides **5** were used without further purification (work-up) in the reduction step. For characterization the crude products are purified by shortpath distillation.

(2*S*,3a'*R*,6a'*R*)-(Hexahydro-cyclopenta[b]pyrrole-1'-yl)-pyrrolidin-2-yl-methanone (2*S*,3a'*R*,6a'*R*)-5d: starting material: 13.58 g (39.7 mmol) **4d**; yield: 7.55 g (91.5 %); $[\alpha]_D^{20} = -181.7$ (c = 1.11, $CHCl_3$); IR (NaCl): ν = 3480-3260 cm^{-1} (NH), 1710-1580 (C=O); ^{1}H-NMR ($CDCl_3$): δ = 1.05–2.0 (5m, 14H, 1x H3a', 2x H4', 2x H5', 2x H6', N$\underline{H}$, 2x H3, 2x H4, 2x H3'), 2.4-2.57 (m, 1H, 1x H2'), 3.08-3.27, 3.27-3.52, 3.86-4.09 (3m, 5H, 1x H2', 2x H5, H6a', H2); ^{13}C-NMR ($CDCl_3$): δ (major rotamer) = 14.37 (C2), 24.81, 26.02, 30.67, 31.62, 33.31, 34.86 (C3', C4', C5', C6', C3, C4), 40.88 (C3a'), 45.98, 59.17 (C4, C2'), 62.72 (C6a'), 154.42 (CON); δ (minor rotamer) = 14.37 (C2), 25.10, 26.24, 29.16, 30.44, 30.96, 34.11 (C3', C4', C5', C6', C3, C4), 42.87 (C3a'), 45.31, 59.17 (C4, C2'), 61.56 (C6a'), 154.35 (CON); MS (CI, *i*-butane): 209 (MH^+, 100 %), 70

(C_4H_8N, 16 %), 110 ($C_7H_{12}N$, 9 %); Anal. calc. for $C_{12}H_{20}N_2O$ (208.3): C, 69.19; H, 9.68; N, 13.45; found: C, 69.11; H, 9.46; N, 13.19.

(3a'*R*,6a'*R*,2*R*,3a*R*,6a*R*)-(Hexahydro-cyclopenta[b]-1'-yl)-(octahydro-cyclopenta[b]pyrrole-2-yl)-methanone (3a'*R*,6a'*R*,2*R*,3a*R*,6a*R*)-5e: starting material: 8.8 g (23 mmol) **4e**; yield: 5.6 g (97.9 %); $[\alpha]_D^{20}$ = – 61.1 (*c* = 1.94, $CHCl_3$); IR (NaCl): ν = 3480-3200 cm^{-1} (NH), 1670 (C=O); ^{1}H-NMR ($CDCl_3$): δ = 0.94–1.91 (5m, 15H, 1x H3a', 2x H4', 2x H5', 2x H6', 1x H3a, 2x H4, 2x H5, 2x H6, NH), 2.0-2.26 (m, 0.5H, 0.5x H3'), 2.34-2.6 (m, 1.5H, 1.5x H3'), 3.0-3.2 (m, 1H, 1x H3), 3.2-3.46, 3.46-3.73 (2m, 3H, 1x H3, 0.4x H2', 1.6x H2'), 3.8-4.06 (m, 2.6H, 1x H6a', 1x H6a, 0.6x H2), 4.06-4.23 (m, 0.4H, 0.4x H2); ^{13}C-NMR ($CDCl_3$): δ = 14.44 (C2), 24.87, 29.58, 30.07, 30.76, 31.69, 33.34, 34.19, 46.06 (C3', C4', C5', C6', C3, C4, C5, C6), 41.98, 42.96 (C3a', C3a), 60.22 (C2'), 62.15, 62.80 (C6a', C6a), 154.54 (CON); MS (CI, *i*-butane): 249 (MH^+, 100); Anal. calc. for $C_{15}H_{24}N_2O$ (248.4): C, 72.54; H, 9.74; N, 11.28; found: C, 72.12; H, 9.31; N, 10.91.

1,2-Diamines: (1*S*,3a'*R*,6a'*R*)-**6a**, (*all-R*)-**6b**, (*all-R*)-**6c**, (2*S*,3a'*R*,6a'*R*)-**6d**, (*all-R*)-**6e**

General Procedure III:

A solution of the amides (2*S*,3a'*R*,6a'*R*)-**5d** and (2*R*,3a*R*,6a*R*,3a'*R*,6a'*R*)-**5e** (40 mmol), respectively (1*S*,3a'*R*,6a'*R*)-**4a** and (1*R*,3a'*R*,6a'*R*)-**4b**, (1*R*,3a'*R*,6a'*R*)-**4c** (20 mmol) is added portionwise over 20 min, with vigorous stirring to a suspension of $LiAlH_4$ (12.2 g, 320 mmol) in dry THF (450 mL) at room temperature. The reaction mixture is then heated under reflux for 18 h. The heating bath is removed and 10 % aqueous NaOH and water are added successively to reaction mixture at room temperature. After a further 2 h stirring under reflux the whole is filtered. The filtrate and THF washings are combined, dried over $MgSO_4$ and the solvent removed *in vacuo* to give slightly yellow oils as crude products. The residues are distilled with fractionating affording the analytically pure 1,2-Diamines.

(1*S*,3a'*R*,6a'*R*)-[1-Benzyl-2-(hexahydro-cyclopenta[b]pyrrole-1'-yl)-ethyl]-methyl-amine (1*S*,3a'*R*,6a'*R*)-6a: starting material: 16.43 g (41.9 mmol) amide **4a**; yield: 7.5 g (69.3 %); b.p.(0.001 mbar): 110 °C; $[\alpha]_D^{20}$ = – 37 (*c* = 3.0, Et_2O); IR (NaCl): ν = 3400-3350 cm^{-1} (NH); ^{1}H-NMR ($CDCl_3$): δ = 1.2–1.67 (3m, 7H, H3a', 2x H4', 2x H5', 2x H6'), 1.73-1.95 (m, 1H, H3'), 2.03-2.2 (m, 1H, H3'), 2.27-2.53 (m, 6H, CH_3, 2x H2', 1x H1), 2.60–2.77 (m, 4H, $C\underline{H}_2Ph$, 2x H2), 2.8-2.9 (m, 1H, H6a'), 7.1-7.23 (m, 5H, aromatic H); ^{13}C-NMR ($CDCl_3$): δ = 24.28, 32.25, 32.82, 32.94 (C3', C4', C5', C6'), 34.01, (CH_3), 38.88, (CH_2Ph), 42.14 (C3a'), 55.59, 59.41 (C2', C2), 59.89, 70.04 (C6a', C1), 125.65, 127.96, 129.13 (aromatic C), 139.46 (q. aromatic C), MS (CI, *i*-butane): 260 (MH^+, 100 %), 124 ($C_7H_{12}NCH_2$, 18%); Anal. calc. for $C_{17}H_{26}N_2$ (258.4): C, 79.02; H, 10.14; N, 10.84; found: C, 79.13; H, 10.19; N, 10.91.

(1*R*,3a'*R*,6a'*R*)-[2-(Hexahydro-cyclopenta[b]pyrrole-1'-yl)-1-phenyl-ethyl]-methyl-amine (1*R*,3a'*R*,6a'*R*)-6b: starting material: 9.68 g (25.6 mmol) amide **4b**; yield: 2.7 g (43.2 %); b.p.(0.001 mbar): 93 °C; m.p.: 46 °C; $[\alpha]_D^{20}$ = – 141.9 (*c* = 1.05, Et_2O); IR (NaCl): ν = 3450-3350 cm^{-1} (NH); ^{1}H-NMR ($CDCl_3$): δ = 1.33–1.85 (3m, 7H, H3a', 2x H4', 2x H5', 2x H6'), 2.05-2.2 (m, 2H, 2x H3'), 2.33-2.44 (m, 1H, H2'), 2.38 (s, 3H, CH_3), 2.5-2.63 (m, 1H, H2'), 2.8-2.9 (m, 2H, 2x H2), 3.13-3.2 (m, 1H, H6a'), 3.6-3.7 (dd, *J* = 3.07 Hz, 11.4 Hz, 1H, H1), 7.28-7.5 (m, 5H, aromatic H); ^{13}C-NMR ($CDCl_3$): δ = 23.94, 32.04, 32.52, 33.47 (C3', C4', C5', C6'), 34.68 (CH_3), 41.24 (C3a'), 53.52, 62.41 (C2', C2), 63.79, 69.74 (C6a', C1), 126.84, 127.22, 128.07 (aromatic C), 142.59 (q. aromatic C); MS (CI, *i*-butane): 124 ($C_7H_{12}NCH_2$, 100 %), 245 (MH^+, 39 %); Anal. calc. for $C_{16}H_{24}N_2$ (244.4): C, 78.64; H, 9.9; N, 11.46; found: C, 78.35; H, 10.09; N, 11.30.

(1*R*,3a'*R*,6a'*R*)-[1-Cyclohexa-1'',4''-dienyl-2-(hexahydro-cyclopenta[b]pyrole-1'-yl)-ethyl]-methyl-amine (1*R*,3a'*R*,6a'*R*)-6c: starting material: 9.25 g (24.3 mmol) amide **4c**; yield: 2.75 g (46 %); b.p.(0.001 mbar): 99 °C; m.p.: 29 °C; $[\alpha]_D^{20} = -121.8$ ($c = 1.16$, Et_2O); IR (NaCl): $\nu = 3400\text{-}3320\ cm^{-1}$ (NH); ^{1}H-NMR ($CDCl_3$): δ = 1.2–1.68 (m, 8H, H3a', 2x H4', 2x H5', 2x H6', NHCH$_3$), 1.9-2.03 (m, 2H, 2x H3'), 2.03-2.98 (m, 2H, 2x H2'), 2.29 (s, 3H, CH_3), 2.4-2.64 (2m, 7H, 2x H2, 2x H3'', 2x H6'', H1), 2.89-3.04 (m, 1H, H6a'), 5.6-5.8 (m, 3H, H1'', H4'', H5''); ^{13}C-NMR ($CDCl_3$): δ = 23.85, 24.75, 26.44, 31.99, 32.45, 33.39 (C3', C4', C5', C6', C3'', C6''), 34.42 (CH_3), 41.17 (C3a'), 53.43, 58.79 (C2', C2), 65.24, 69.77 (C6a', C1), 121.04, 123.75, 124.42 (olefinic C), 134.93 (q. olefinic C); MS (CI, *i*-butane): 247 (MH^+, 100 %), 124 ($C_7H_{12}NCH_2$, 42 %); Anal. calc. for $C_{16}H_{26}N_2$ (246.4): C, 77.99; H, 10.64; N, 11.37; found: C, 77.38; H, 11.06; N, 11.21.

(2*S*,3a'*R*,6a'*R*)-1'-(Pyrrolidin-2-yl-methyl)-octahydro-cyclopenta[b]pyrrole (2*S*,3a'*R*,6a'*R*)-6d: starting material: 6 g (28.8 mmol) amide **5d**; yield: 2.14 g (38.3 %); b.p. (0.003 mbar): 81 °C; $[\alpha]_D^{20} = -37.9$ ($c = 4.73$, $CHCl_3$); IR (NaCl): ν = 3420-3200 cm^{-1} (NH); ^{1}H-NMR ($CDCl_3$): δ = 1.0–1.57 (4m, 10H, H3a', 2x H4', 2x H5', 2x H6'), 1.6-1.77 (1m, 2H), 1.91-2.06 (1m, 1H, 1x H3'), 2.1-2.34 (1m, 3H), 2.4-2.53 (1m, 1H, H2), 2.53-2.84 (1m, 4H), 2.91-3.06 (1m, 1H, H6a'); ^{13}C-NMR ($CDCl_3$): δ = 24.03, 24.65, 29.74, 32.11, 32.58, 32.93 (C3', C4', C5', C6', C3, C4), 41.71 (C3a'), 45.78 (C5), 55.34 (C2'), 57.12 (C6a'), 60.8 (C1''), 69.9 (C2); MS (CI, *i*-butane): 195 (MH^+, 81 %), 124 ($C_7H_{12}NCH_2$, 9 %), 110 ($C_7H_{12}N$, 2 %); Anal. calc. for $C_{12}H_{22}N_2$ (194.3): C, 74.1; H, 11.41; N, 14.42; found: C, 74.05; H, 11.12; N, 13.98.

(3a'*R*,6a'*R*,2*R*,3a*R*,6a*R*)-(Hexahydro-cyclopenta[b]pyrrole-1'-yl-methyl)-octahydro-cyclopenta[b]pyrrole (2*R*,3a*R*,6a*R*,3a'*R*,6a'*R*)-6e: starting material: 5.6 g (22.5 mmol) amide **5e**, yield: 1.03 g (19.6 %); b.p.(0.003 mbar): 87 °C; $[\alpha]_D^{20} = -34.1$ ($c = 3.22$, $CHCl_3$); IR (NaCl): ν = 3420-3240 cm^{-1} (NH); ^{1}H-NMR ($CDCl_3$): δ = 0.7–0.87 (m, 1H, NH), 1.15-1.66 (m, 13H, 1x H3a', 2x H4', 2x H5', 2x H6', 2x H4, 2x H5, 2x H6), 1.77-2.05 (2m, 4H, 2x H3', 2x H3), 2.2-2.3 (m, 1H, H3a'), 2.32-2.47 (m, 2H, 2x H2'), 2.5-2.55 (m, 1H, 1x H1''), 2.63-2.73 (m, 1H, 1xH1''), 2.83-3.0 (m, 2H, H6a', H6a), 3.45-3.56 (m, 1H, H2); ^{13}C-NMR ($CDCl_3$): δ = 23.51, 24.07, 32.08, 32.59, 32.77, 33.06, 34.17, 39.47 (C3', C4', C5', C6', C3, C4, C5, C6), 41.5, 42.29 (C3a', C3a), 54.77 (C2'), 60.33 (C1''), 58.91, 62.55 (C6a', C6a), 70.04 (C2); MS (CI, *i*-butane): 235 (MH^+, 100 %), 124 ($C_7H_{12}NCH_2$, 16 %), 110 ($C_7H_{12}N$, 3 %); Anal. calc. for $C_{15}H_{26}N_2$ (234.4): C, 76.87; H, 11.18; N, 11.95; found: C, 76.25; H, 11.25; N, 11.68.

(3a'*R*,6a'*R*)-*o*-(Hexahydrocyclopenta[b]pyrrole-1'-carbonyl)-benzoic acid methyl ester (3a'*R*,6a'*R*)-7: The solution of 76 g (0.42 mol) phthalic acid monomethylester and 210 mL (2.93 mol) thionylchloride was heated under reflux for 1 h. Excess thionylchloride was removed under reduced pressure.The residue was diluted in 30 mL toluene and the solvent was evaporated under reduced pressure. This procedure was repeated two times to remove the thionylchloride completely. The obtained 81.4 g (0.42 mol) of the crude acid chloride were used without further purification in the next step. 46 g (0.41 mol) (*all-R*)-octahydrocyclopenta[b]pyrrole were diluted in 800 mL dry toluene and 59 mL (0.42 mol) triethylamine was added. To this colourless solution 81.4 g (0.42 mol) of the prepared acidchloride diluted in 200 mL dry toluene was added dropwise at 0 °C (ice-salt bath). During the addition a colourless voluminous precipitate of triethylamine-hydrochloride was observed. After the addition the reaction mixture was allowed to warm to room temperature and was stirred for 24 h. After this period 250 mL H_2O were added. The organic layer was seperated and then extracted with 2x 200 mL 0.5 N HCl, 200 mL H_2O, 2x 125 mL 2N NaOH and again with 200 mL H_2O. Finally the organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The obtained crude product, an orange oil, was of satisfactory purity (^{1}H-NMR pure) for use in further reactions. An analytical

sample was purified by flash chromatography (eluent: EtOAc / *n*-hexane 7:3, R_f-value: 0.35) to give a colourless solid after removal of the solvent.

Yield: 108.8 g (96 %, crude product); m.p.: 44 °C; $[\alpha]_D^{20}$ = -120.4 (c = 1, $CHCl_3$); IR (KBr): ν = 1710 cm^{-1} (C=O, ester), 1620 (C=O, amide); ^{1}H-NMR ($CDCl_3$): at 22 °C rotamers in an ratio of 36:64 were observed, δ = 1.23-2.17 (m, 8H, 1xH2′, 1xH3a′, 2xH4′, 2xH5′, 2xH6′), 2.73-2.78 (m, 1H, H3′), 3.11-3.15 (m, 1.28H, 0.64xH3′, 0.64xH2′), 3.45-3.54 (m, 0.36H, 0.36xH3′), 3.80-3.83 (m, 0.36H, 0.36xH2′),3.87 (s, 3H, OCH_3), 4.02-4.13 (m, 0.36H, 0.36xH6a′), 4.51-4.57 (m, 0.64H, 0.64xH6a′), 7.29-7.59 (m, 3H, aromatic H), 7.98-8.04 (m, 1H, aromatic H); ^{13}C-NMR ($CDCl_3$): at 22 °C rotamers in an ratio of 36:64 were observed, δ (major rotamer) = 25.68, 31.19, 32.07, 33.17 (C3′,C4′,C5′,C6′), 42.06 (C3a′), 48.44 (C2′), 52.22 (OCH_3), 62.51 (C6a′), 126.81, 128.40, 130.34, 132.71 (aromatic C), 139.96, 137.77 (q. aromatic C), 166.17, 168.47 (N-C=O, $\underline{C}O_2CH_3$); δ (minor rotamer) = 25.46, 29.94, 31.61, 34.20 (C3′,C4′,C5′,C6′), 43.45 (C3a′), 45.34 (C2′), 52.87 (OCH_3), 63.99 (C6a′), 127.47, 129.65, 132.28, 132.42 (aromatic C), 137.56, 139.75 (q. aromatic C), 166.45, 168.85 (N-C=O, $\underline{C}O_2CH_3$); MS (CI, *i*-butane): 274.4 (MH^+, 100 %), 547.6 (M_2H^+, 19 %); Anal. calc. for $C_{16}H_{19}NO_3$ (273.3): C, 70.31; H, 7.01; N, 5.12. found: C, 70.15; H, 6.93; N, 5.06.

(3a′*R*,6a′*R*)-[*o*-(Hexahydro-cyclopenta[b]pyrrole-1′-yl-methyl)-phenyl]-methanol (3a′*R*,6a′*R*)-8:

A solution of 27.3 g (100 mmol) methyl ester (3a′*R*,6a′*R*)-7 in 200 mL dry THF is added portionwise over 20 min. with vigourous stirring to a suspension of 30.4 g (0.8 mol) $LiAlH_4$ in 500 mL dry THF at room temperature under argon atmosphere. The reaction mixture is then heated under reflux for 18 h. The heating bath is removed and 10 % aqueous NaOH and water are added succesively to reaction mixture at room temperature. After further 2 h stirring under reflux the white residue is filtered off and washed with THF. The filtrate and the THF washings are combined, dried over $MgSO_4$ and the solvent is removed *in vacuo* to give a pale yellow oil as crude product, which crystallized over night at 4 °C. Recristallization from MTBE gives a white solid.

Yield: 15.96 g (69 %); m.p.: 45 °C; $[\alpha]_D^{20}$ = -24.6 (c = 1, $CHCl_3$); IR (KBr): ν = 3100-3370 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$): δ = 1.24-1.68 (m, 7H, 1xH3a′, 2xH4′, 2xH5′, 2xH6′), 1.90-2.00 (m, 1H, H3′), 2.06-2.15 (m, 1H, H3′), 2.60-2.73 (m, 2H, 2xH2′), 2.95-3.00 (m, 1H, H6a′), 3.41 (d, ^{2}J = 12.1 Hz, 1H, Ar-C$\underline{H}_2$-OH), 4.08 (d, ^{2}J = 12.1 Hz, 1H, Ar-C$\underline{H}_2$-OH), 4.47 (d, ^{2}J = 12.0 Hz, 1H, Ar-C$\underline{H}_2$-N), 4.78 (d, ^{2}J = 12.0 Hz, 1H, Ar-C$\underline{H}_2$-N), 7.21-7.35 (m, 4H, aromatic H); ^{13}C-NMR ($CDCl_3$): δ = 24.34, 31.66, 31.75, 32.89 (C3′, C4′,C5′, C6′), 42.48 (C3a′), 54.43, 59.17, 64.98, 70.61 (C2′, C6a′, Ar-$\underline{C}H_2$-OH, Ar-$\underline{C}H_2$-N), 127.79, 128.22, 129.70, 130.24 (aromatic C), 137.87, 141.27 (q. aromatic C); MS (CI, *i*-butane): 214.3 (MH^+-H_2O, 100 %), 232.4 (MH^+, 78 %); Anal. calc. for $C_{15}H_{21}NO$ (231.3): C, 77.88; H, 9.15; N, 6.05; found: C, 77.74; H, 9.21; N, 5.96.

(3a′*R*,6a′*R*)-o-(Hexahydrocyclopenta[b]pyrrole-1′-ylmethyl)-benzaldehyde (3a′*R*,6a′*R*)-9:

According to the procedure of *D. Swern*[15] 10.2 mL (119 mmol) oxalylchloride is dissolved in 200 ml dry CH_2Cl_2 under argon atmosphere. This solution is cooled to -80 °C and a solution of 16.9 mL (238 mmol) dry DMSO in 40 mL dry CH_2Cl_2 is added dropwise in the way that a temperature of -60 °C is not exceeded. The clear solution is stirred 30 min. at -70 °C. Now a solution of 25 g (108 mmol) (3a′*R*,6a′*R*)-8 in 60 mL dry CH_2Cl_2 is added dropwise again in the way that a temperature of -60 °C is not exceeded. The mixture is stirred for 30 min. at -70 °C and 75 mL (0.54 mol) triethylamine is added (T < -60 °C). After 10 min. of stirring the reaction mixture is allowed to warm to room temperature. 100 mL water is added the phases were separated. The aqueous layer is extracted two times with additional 50 mL CH_2Cl_2. The organic layers are combined and

dried over $MgSO_4$. The filtered solution is fully concentrated in a rotary evaporator and the residue, an orange oil, is cristallized from MTBE / *n*-hexane at 4 °C to give a pale yellow solid.
Yield: 21.79 g (88 %); m.p.: 56 °C; $[\alpha]_D^{20}$ = -66.8 (c = 1, $CHCl_3$); IR (KBr): ν = 1680 cm^{-1} (C=O); ^{1}H-NMR ($CDCl_3$): δ = 1.16-1.68 (m, 7H, 1xH3a', 2xH4', 2xH5', 2xH6'), 1.84-1.94 (m, 1H, H3'), 2.01-2.10 (m, 1H, H3'), 2.47-2.66 (m, 2H, 2xH2'), 2.90-2.95 (m, 1H, H6a'), 3.57 (d, ^{2}J = 13.2 Hz, 1H, Ar-C$\underline{H}_2$-N), 4.27 (d, ^{2}J = 13.2 Hz, 1H, Ar-C$\underline{H}_2$-N), 7.35-7.86 (m, 4H, aromatic H), 10.50 (s, 1H, CHO); ^{13}C-NMR ($CDCl_3$): δ = 24.35, 31.98, 32.18, 33.37 (C3', C4',C5', C6'), 42.09 (C3a'), 54.19, 56.48, 70.13 (C2', C6a', Ar-$\underline{C}H_2$-N), 127.48, 128.52, 130.17, 133.24 (aromatic C), 134.81, 142.63 (q. aromatic C), 192.31 (CHO); MS (CI, *i*-butane): 230.4 (MH^+, 100 %), 246.3 (MH^++1/2 O_2, 82 %), 475.5 (M_2H^++1/2 O_2, 18 %); Anal. calc. for $C_{15}H_{19}NO$ (229.3): C, 78.56; H, 8.35; N, 6.11; found: C, 78.39; H, 8.29; N, 5.98.

δ-Amino-alcohols: (-)-(1*R**,3a'*R*,6a'*R*)-**10a**, (-)-(1*R**,3a'*R*,6a'*R*)-**10b**, (-)-(1*R**,3a'*R*,6a'*R*)-**10c**, (-)-(1*R**,3a'*R*,6a'*R*)-**10d**, (+)-(1*S**,3a'*R*,6a'*R*)-**10d**, (-)-(1*R**,3a'*R*,6a'*R*)-**10e**, (+)-(1*S**,3a'*R*,6a'*R*)-**10e**; **General Procedure IV**

A *Grignard* reagent is prepared in the usual way from 0.58 g (24 mmol) magnesium powder and 24 mmol of the alkyl- respectively aryl halogenide in 20 mL dry diethyl ether under argon atmosphere. To this reaction mixture a solution of 2.75 g (12 mmol) aldehyd (3a'*R*,6a'*R*)-**9** in a mixture of 30 mL dry THF / dry diethyl ether (1:2) is added dropwise at -10 °C (ice-salt bath). The mixture is stirred 3 h at -10 °C and 12 h at room temperature. The reaction mixture is hydrolysed with 20 mL saturated NH_4Cl solution at -10 °C and is allowed to warm to room temperature. After the addition of 50 mL water the two phases are separated and the aqueous layer is extracted three times with 40 mL CH_2Cl_2 each time. The pale yellow organic layer is fully concentrated *in vacuo* and the residue is dissolved in 50 mL CH_2Cl_2. The combined CH_2Cl_2 phases are washed with 60 mL brine and dried over $MgSO_4$. The solution is fully concentrated in a rotary evaporator. The crude products are yellow to brown oils. In a few cases these oils cristallize overnight. The determination of the diastereomeric ratio is made by examination of an ^{1}H-NMR spectrum of the crude product. The obtained crude products are purified by flash chromatography. The individual work-up is described below.

(-)-(1*R,3a'*R*,6a'*R*)-1-[o-(Hexahydrocyclopenta[b]pyrrole-1'-ylmethyl)-phenyl]-ethanol**

(-)-(1*R,3a'*R*,6a'*R*)-10a:** starting material for Grignard reagent: 1.5 mL (24 mmol) iodomethane. The crude product is a brown oil. Diastereomeric ratio (^{1}H-NMR): 54:46; work-up: purification by chromatography (eluent: *n*-hexane / EtOAc 8 : 2 with 2 % triethylamine, R_f-value: 0.41) gives a pale yellow oil as the major diastereomer; yield: 0.91 g (31 %); $[\alpha]_D^{20}$ = -46.0 (c = 1, $CHCl_3$); IR ($CHCl_3$): ν = 3090-3350 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$): δ = 1.16-2.06 (m, 12H, 1xH3a', 2xH4', 2xH5', 2xH6', 2xH3', CH_3), 2.52-2.64 (m, 2H, 2xH2'), 2.93-2.98 (m, 1H, H6a'), 3.14 (d, ^{2}J = 12.1 Hz, 1H, Ar-C$\underline{H}_2$-N), 4.35 (d, ^{2}J = 12.1 Hz, 1H, Ar-C$\underline{H}_2$-N), 5.07 (q, ^{3}J = 6.6 Hz, 1H, Ar-C$\underline{H}$-OH), 7.19-7.43 (m, 4H, aromatic H); ^{13}C-NMR ($CDCl_3$): δ = 19.78 (CH_3), 24.49, 2x31.56, 32.95 (C3', C4', C5', C6'), 42.28 (C3a'), 53.88, 58.71 (C2', C6a'), 65.23, 70.63 (Ar-$\underline{C}H_2$-N, Ar-$\underline{C}$H-OH), 124.96, 127.10, 128.07, 130.77 (aromatic C), 137.12, 144.10 (q. aromatic C); MS (CI, *i*-butane): 246 (MH^+, 100 %), 228 (MH^+- H_2O, 26 %); Anal. calc. for $C_{16}H_{23}NO$ (245.4): C, 78.32; H, 9.45; N, 5.71; found: C, 78.24; H, 9.34; N, 5.60.

(-)-(1*R,3a'*R*,6a'*R*)-1-[o-(Hexahydrocyclopenta[b]pyrrole-1'-yl-methyl)-phenyl]-propanol**

(-)-(1*R,3a'*R*,6a'*R*)-10b:** starting material for Grignard reagent: 1.8 mL (24 mmol) ethylbromide. The crude product is a brown oil. Diastereomeric ratio (^{1}H-NMR): 59:41; work-up: purification by chromatography

(eluent: *n*-hexane / EtOAc 8 : 2 with 2 % triethylamine, R_f-value: 0.41) gives a pale yellow oil as the major diastereomer; yield: 0.82 g (26 %); $[\alpha]_D^{20}$ = -27,0 (c = 1, $CHCl_3$); IR ($CHCl_3$): ν = 3080-3330 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$): δ = 1.04-1.08 (m, 3H, CH_3), 1.21-2.08 (m, 11H, 1xH3a', 2xH4', 2xH5', 2xH6', 2xH3', $C\underline{H}_2CH_3$), 2.57-2.62 (m, 2H, 2xH2'), 2.94-2.99 (m, 1H, H6a'), 3.25 (d, ^{2}J = 12.1 Hz, 1H, Ar-$C\underline{H}_2$-N), 4.28 (d, ^{2}J = 12.1 Hz, 1H, Ar-$C\underline{H}_2$-N), 4.69 (dd, ^{3}J = 7.15 und 6.6 Hz, 1H, Ar-C<u>H</u>-OH), 7.20-7.32 (m, 4H, aromatic H); ^{13}C-NMR ($CDCl_3$): δ = 11.23 (CH_3), 24.37, 26.81, 2x31.62, 32.95 (C3', C4', C5', C6', $\underline{C}H_2CH_3$), 42.31 (C3a'), 54.06, 58.87 (C2', C6a'), 70.57, 71.80 (Ar-$\underline{C}H_2$-N, Ar-<u>C</u>H-OH), 125.67, 126.93, 128.00, 130.77 (aromatic C), 137.35, 143.35 (q. aromatic C); MS (CI, *i*-butane): 260 (MH^+, 100 %), 242 (MH^+- H_2O, 21 %); Anal. calc. for $C_{17}H_{25}NO$ (259.4): C, 78.72; H, 9.71; N, 5.40; found: C, 78.56; H, 9.74; N, 5.31.

(-)-(1*R,3a'*R*,6a'*R*)-1-[o-(Hexahydrocyclopenta[b]pyrrole-1'-yl-methyl)-phenyl]-2-phenylethanol (-)-(1*R**,3a'*R*,6a'*R*)-10c:** starting material for Grignard reagent: 2.8 mL (24 mmol) benzylbromide. The crude product is a yellow oil. Diastereomeric ratio (^{1}H-NMR): 59:41; work-up: purification by chromatography (eluent: *n*-hexane / EtOAc 8 : 2, R_f-value: 0.28) gives a pale yellow oil as the major diastereomer; yield: 0.54 g (14 %); $[\alpha]_D^{20}$ = -43.5 (c = 1, $CHCl_3$); IR ($CHCl_3$): ν = 3090-3250 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$): δ = 1.15-2.13 (m, 9H, 1xH3a', 2xH4', 2xH5', 2xH6', 2xH3'), 2.53-2.67 (m, 2H, 2xH2'), 2.92-2.97 (m, 1H, H6a'), 3.18-3.35 (m, 3H, Ph-$C\underline{H}_2$, 1xAr-$C\underline{H}_2$-N), 4.15 (d, ^{2}J = 12.1 Hz, 1H, Ar-$C\underline{H}_2$-N), 5.13 (dd, ^{3}J = 5.49 und 6.05 Hz, 1H, Ar-C<u>H</u>-OH), 7.14-7.37 (m, 9H, aromatic H); ^{13}C-NMR ($CDCl_3$): δ = 24.24, 2x31.59, 32.87 (C3', C4', C5', C6'), 40.73, 42.29 (C3a', Ph-$\underline{C}H_2$), 54.19, 58.93 (C2', C6a'), 70.41, 71.55 (N-$\underline{C}H_2$-Ar, Ar-<u>C</u>H-OH), 125.77-130.78 (aromatic C), 137.01, 139.59, 143.12 (q. aromatic C); MS (CI, *i*-butane): 322 (MH^+, 100 %), 304 (MH^+- H_2O, 24 %); Anal. calc. for $C_{22}H_{27}NO$ (321.5): C, 82.20; H, 8.47; N, 4.36; found: C, 82.01; H, 8.45; N, 4.25.

(-)-(1*R,3a'*R*,6a'*R*)-1-[o-(Hexahydrocyclopenta[b]pyrrole-1'-yl-methyl)-phenyl]-naphthalen-1-yl-methanol (-)-(1*R**,3a'*R*,6a'*R*)-10d:** starting material for Grignard reagent: 3.4 mL (24 mmol) 1-bromonaphthalene. The usual work-up from the general procedure IV is changed: After hydrolysis the phases are separated and the aqueous phase is extracted 3 times with 40 mL diethyl ether. The combined yellow organic phases are washed with brine and then concentrated *in vacuo*. The residue is dissolved in 40 mL methanol and 50 mL 2N HCl and is stirred for 30 min. at room temperature. The solution is extracted three times with 60 mL of PE 40/60. 2 N NaOH is added to the aqueous phase till pH = 10 and the solution is extracted 3 times with 40 mL of CH_2Cl_2. The combined yellow CH_2Cl_2 phases are washed with brine, dried over $MgSO_4$ and fully concentrated *in vacuo*. The crude product is a beige solid. Diastereomeric ratio (^{1}H-NMR): 51:49; work-up: purification by chromatography (eluent: *n*-hexane / EtOAc 8 : 2, R_f-value: 0.38) gives a colourless solid as the major diastereomer; yield: 1.05 g (24 %); m.p.: 69-71 °C; $[\alpha]_D^{20}$ = -98.7 (c = 1, $CHCl_3$); IR (KBr): ν = 3060-3260 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$): δ = 1.24-2.16 (m, 9H, 1xH3a', 2xH4', 2xH5', 2xH6', 2xH3'), 2.60-2.69 (m, 2H, 2xH2'), 3.04-3.11 (m, 1H, H6a'), 3.30 (d, ^{2}J = 12.1 Hz, 1H, Ar-$C\underline{H}_2$-N), 4.73 (d, ^{2}J = 12.1 Hz, 1H, Ar-$C\underline{H}_2$-N), 6.56 (m, 1H, aromatic H), 6.74 (s, 1H, Ar-C<u>H</u>-OH), 6.96-8.04 (m, 10H, aromatic H); ^{13}C-NMR ($CDCl_3$): δ = 24.72, 2x31.82, 33.04 (C3', C4', C5', C6'), 42.37 (C3a'), 54.13, 59.12 (C2', C6a'), 69.66, 70.96 (Ar-$\underline{C}H_2$-N, Ar-<u>C</u>H-OH), 124.08-128.67 (aromatic C), 130.66, 133.55, 136.81, 137.56, 144.21 (q. aromatic C); MS (CI, *i*-butane): 358 (MH^+, 100 %), 340 (MH^+- H_2O, 26 %); Anal. calc. for $C_{25}H_{27}NO$ (357.5): C, 83.99; H, 7.61; N, 3.92; found: C, 83.89; H, 7.55; N, 3.87.

(+)-(1*S,3a'*R*,6a'*R*)-1-[o-(Hexahydrocyclopenta[b]pyrrole-1'-yl-methyl)-phenyl]-naphthalen-1-yl-methanol (+)-(1*S**,3a'*R*,6a'*R*)-10d:** starting material for Grignard reagent: 3.4 mL (24 mmol) 1-bromonaphthalene. work-up: see work-up for major diastereomer (-)-(*1Ξ,3a'R,6a'R*)-**10d**. The crude product is a beige solid. Diastereomeric ratio (^{1}H-NMR): 51:49; work-up: purification by chromatography (eluent: *n*-hexane / EtOAc 8 : 2, R_f-value: 0.18) gives a colourless solid as the minor diastereomer; yield: 0.3 g (7 %); m.p.: 183-185 °C (decomposes); $[\alpha]_D^{20}$ = +62.0 (c = 1, $CHCl_3$); IR (KBr): ν = 3060-3360 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$): δ = 0.96-1.65 (m, 8H, 1xH3a', 2xH4', 2xH5', 2xH6', 1xH3'), 1.95-2.06 (m, 1H, H3'), 2.50-2.58 (m, 1H, H2'), 2.69-2.75 (m, 1H, H2'), 3.09-3.18 (m, 1H, H6a'), 3.57 (d, ^{2}J = 12.1 Hz, 1H, Ar-C$\underline{H}_2$-N), 4.55 (d, ^{2}J = 12.1 Hz, 1H, Ar-C$\underline{H}_2$-N), 6.68 (m, 1H, aromatic H), 6.78 (s, 1H, Ar-C$\underline{H}$-OH), 7.06-8.03 (m, 10H, aromatic H); ^{13}C-NMR ($CDCl_3$): δ = 24.36, 31.49, 31.72, 32.71 (C3', C4', C5', C6'), 43.02 (C3a'), 55.61, 59.36 (C2', C6a'), 70.26, 70.56 (Ar-$\underline{C}H_2$-N, Ar-$\underline{C}$H-OH), 124.35-130.33 (aromatic C), 131.04, 133.59, 137.52, 137.77, 144.02 (q. aromatic C); MS (CI, *i*-butane): 358 (MH^+, 100 %), 340 (MH^+- H_2O, 34 %); Anal. calc. for $C_{25}H_{27}NO$ (357.5): C, 83.99; H, 7.61; N, 3.92; found: C, 83.90; H, 7.63; N, 3.84.

(-)-(1*R,3a'*R*,6a'*R*)-1-[o-(Hexahydrocyclopenta[b]pyrrole-1'-yl-methyl)-phenyl]-1-o-tolyl-methanol (-)-(1*R**,3a'*R*,6a'*R*)-10e:** starting material for Grignard reagent: 2.9 mL (24 mmol) *o*-bromotoluene. The crude product is a brown oil. Diastereomeric ratio (^{1}H-NMR): 54:46; work-up: purification by chromatography (eluent: *n*-hexane / EtOAc 8 : 2, R_f-value: 0.47) gives a colourless solid as the major diastereomer; yield: 1.4 g (36 %); m.p.: 107 °C; $[\alpha]_D^{20}$ = -61.5 (c = 1, $CHCl_3$); IR (KBr): ν = 3060-3320 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$): δ = 1.30-2.14 (m, 12H, 1xH3a', 2xH4', 2xH5', 2xH6', 2xH3', Ar-C$\underline{H}_3$), 2.65-2.71 (m, 2H, 2xH2'), 3.03-3.08 (m, 1H, H6a'), 3.24 (d, ^{2}J = 12.1 Hz, 1H, Ar-C$\underline{H}_2$-N), 4.60 (d, ^{2}J = 12.1 Hz, 1H, Ar-C$\underline{H}_2$-N), 6.20 (s, 1H, Ar-C$\underline{H}$-OH), 6.64-6.68 (m, 1H, aromatic H), 7.11-7.54 (m, 6H, aromatic H), 7.84-7.89 (m, 1H, aromatic H); ^{13}C-NMR ($CDCl_3$): δ = 19.22 (Ar-$\underline{C}H_3$), 24.66, 31.70, 31.75, 32.97 (C3', C4', C5', C6'), 42.30 (C3a'), 54.03, 58.98 (C2', C6a'), 69.62, 70.86 (Ar-$\underline{C}H_2$-N, Ar-$\underline{C}$H-OH), 125.91-130.60 (aromatic C), 134.60, 137.21, 140.27, 143.57 (q. aromatic C); MS (CI, *i*-butane): 322 (MH^+, 100 %), 304 (MH^+- H_2O, 14 %); Anal. calc. for $C_{22}H_{27}NO$ (321.5): C, 82.20; H, 8.47; N, 4.36; found: C, 82.06; H, 8.39; N, 4.28.

(+)-(1*S,3a'*R*,6a'*R*)-1-[o-(Hexahydrocyclopenta[b]pyrrole-1'-yl-methyl)-phenyl]-1-o-tolyl-methanol (+)-(1*S**,3a'*R*,6a'*R*)-10e:** starting material for Grignard reagent: 2.9 mL (24 mmol) *o*-bromotoluene. The crude product is a brown oil. Diastereomeric ratio (^{1}H-NMR): 54:46; work-up: purification by chromatography (eluent: *n*-hexane / EtOAc 8 : 2, R_f-value: 0.15) gives a colourless solid as the minor diastereomer; yield: 0.14 g (4 %); m.p.: 118 °C; $[\alpha]_D^{20}$ = +32.4 (c = 1, $CHCl_3$); IR (KBr): ν = 3070-3290 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$): δ = 0.94-2.02 (m, 12H, 1xH3a', 2xH4', 2xH5', 2xH6', 2xH3', Ar-C$\underline{H}_3$), 2.43-2.70 (m, 2H, 2xH2'), 3.07-3.13 (m, 1H, H6a'), 3.46 (d, ^{2}J = 12.1 Hz, 1H, Ar-C$\underline{H}_2$-N), 4.41 (d, ^{2}J = 12.1 Hz, 1H, Ar-C$\underline{H}_2$-N), 6.17 (s, 1H, Ar-C$\underline{H}$-OH), 6.68-6.72 (m, 1H, aromatic H), 7.12-7.36 (m, 6H, aromatic H), 7.78-7.83 (m, 1H, aromatic H); ^{13}C-NMR ($CDCl_3$): δ = 19.30 (Ar-$\underline{C}H_3$), 24.35, 31.44, 31.66, 32.67 (C3', C4', C5', C6'), 42.99 (C3a'), 55.55, 59.21 (C2', C6a'), 70.17, 70.57 (Ar-$\underline{C}H_2$-N, Ar-$\underline{C}$H-OH), 125.74-130.25 (aromatic C), 134.96, 137.86, 140.36, 143.44 (q. aromatic C); MS (CI, *i*-butane): 322 (MH^+, 100 %), 304 (MH^+- H_2O, 31 %); Anal. calc. for $C_{22}H_{27}NO$ (321.5): C, 82.20; H, 8.47; N, 4.36; found: C, 82.12; H, 8.50; N, 4.31.

General Procedure for catalytic asymmetric addition of benzaldehyde with diethylzinc in the presence chiral 1,2-diamines respectively δ-amino alcohols or their lithium salts:

Unless stated otherwise in the tables, 1 mmol (10 mol%) of the corresponding diamine respectively δ-amino-alcohol as catalyst is diluted in 20 mL dry toluene and cooled to -10 °C under argon atmosphere. If the lithium

salt is required, the equimolar butyllithium ammount is added. 18.2 mL (20 mmol) diethylzinc (1.1 M solution in toluene) is added dropwise over a period of 10 min. After the addition the mixture is allowed to reach room temperature and is stirred for 30 min. Now 10 mmol of freshly distilled benzaldehyde in 10 mL dry toluene is added. Unless stated otherwise in the tables 1 or 2, the yellow solution is stirred 40 h at room temperature. The reaction is quenched with 40 mL 2N HCl at 0 °C, the organic layer is separated and the aqueous layer is extracted 3 times with diethyl ether. The combined organic layers are extracted 3 times with 20 mL 3.9 % sodium hydrogen sulfite solution and washed with saturated sodium hydrogen carbonate and water. After drying over $MgSO_4$ the solvent is evaporated under reduced pressure and the residue is distilled under vaccum to afford the pure secondary alcohol 1-phenyl-1-propanol.

References and Notes

1 Part 8 in the series "Utilization of industrial waste materials".

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