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Synthesis and application of new β-amino alcohols based on the octahydro-cyclopenta[*b*]pyrrole system in the catalytic enantioselective addition of diethylzinc to benzaldehyde

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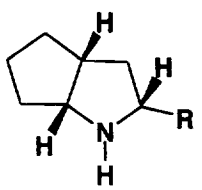
Abstract: Starting from an industrial waste material, the synthesis of a series of new, artificial β-amino alcohol structures (*all-R*)-**6–10** and **13–16** based on the octahydro-cyclopenta[*b*]pyrrole system is presented. These structures were also the subject of studies aimed at developing effective catalysts for enantioselective alkylation by diethylzinc. Attention was focussed on stereochemical and steric aspects of the catalyst (-precursor) structure. Potent chiral ligands have been developed reaching excellent enantioselectivities, e.g. *op*-values up to 99% with predominant formation of the (*R*)-configurated alkylation products. © 1997 Elsevier Science Ltd

Introduction

The design and development of cost-effective catalysts that exhibit high reactivity and enantioselectivity is a challenging endeavour in organic chemistry. In the context with our studies on the utilization of industrial waste materials, we used (*all-R*)-**1a**[1] in the synthesis of new artificial auxiliaries suitably designed for various applications in the enantioselective catalysis (Scheme 1).[2–4]



	R
1a	CO_2CH_2Ph
1b	CO_2H
1c	CH_2OH
1d	$C(Ph)_2OH$

Scheme 1.

Encouraged by the catalytic enantioselectivity induced by some ligands containing the (*all-R*)-octahydro-cyclopenta[*b*]pyrrole system, we were interested in an empirical investigation changing the stereochemical and steric properties of these *sec*- and *tert*-amino alcohol structures systematically.

To obtain information on the structural requirements for a highly stereodifferentiating catalyst structure we modified the (*all-R*)-configuration bicyclic octahydro-cyclopenta[*b*]pyrrole framework by *N*-methylation, variation of the substitution pattern in α-position, ring-size of the cycloalkanol subunit, β-epimerization and diastereoselective ring-expansion to chiral piperidines.

Results and discussion

Sterically constrained β-amino-*tert*-alcohols bearing a cycloalkanol-framework were prepared by conversion of *N*-Boc-amino esters with bifunctional Grignard-reagents. Therefore, the synthesis of related *sec*-amino-*tert*-alcohols[2c,5] was modified to have access to the corresponding novel *tert*-amino structures (*all-R*)-**7**, (*S*)-**13** and (*R*)-**14**.

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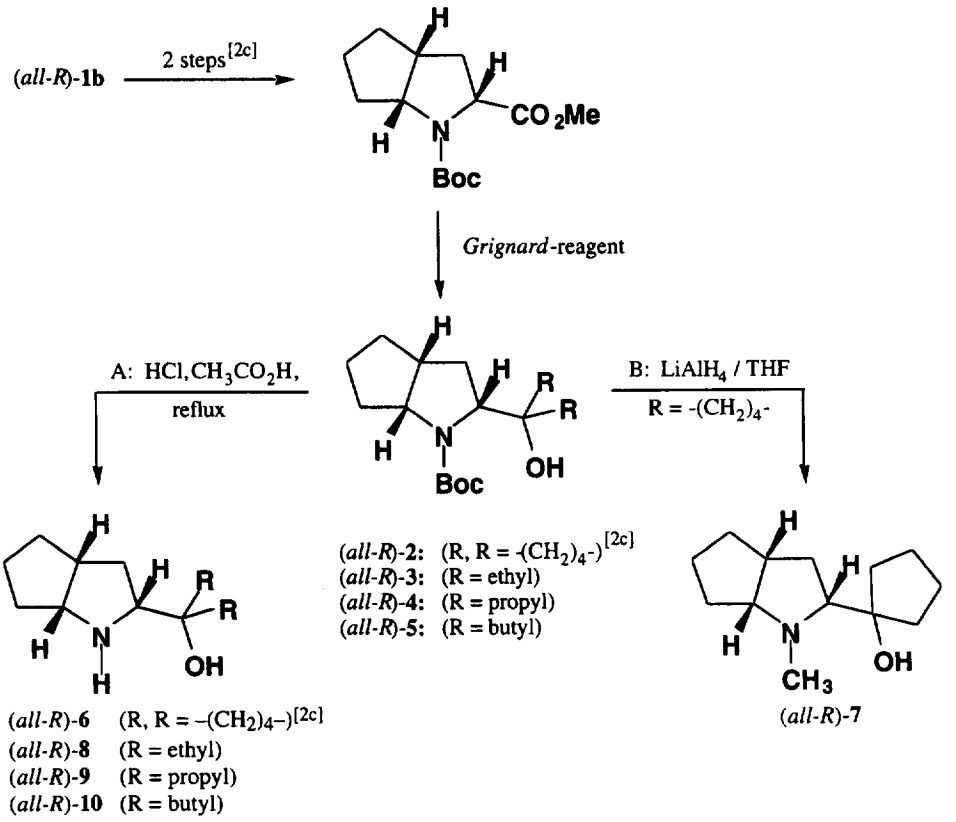
Thus, the *N*-Boc-protected amino alcohol intermediate (*all-R*)-**2** was reduced by treatment with $LiAlH_4$/THF affording the *N*-methylated *tert*-amino-*tert*-alcohol (*all-R*)-**7** in 80% yield (Scheme 2, Grignard-reagent: 1,4-*bis*(bromomagnesio)butane, reaction pathway: B). The reaction pathway A with (*all-R*)-**2** as starting material led to the corresponding *sec*-amino alcohol (*all-R*)-**6**. The same procedure as described for (*all-R*)-**7** was applied for the preparation of compounds (*S*)-**13** and (*R*)-**14** derived from (*S*)-proline and (*R*)-tetrahydro-isochinoline carboxylic acid, respectively.

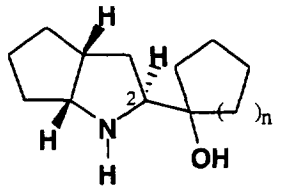


Scheme 2.

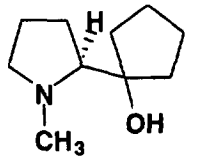
In the next step, we prepared the α-*bis*-ethyl, -propyl and -butyl octahydro-cyclopenta[*b*]pyrrole derivatives (*all-R*)-**8–10** (for R see Scheme 2) in which the rigid cycloalkanol subunit was replaced by two alkyl substituents. Furthermore, diastereomeric ring-expanded piperidine structures **16**,[6] β-epimerized β-amino alcohols (2*S*,3a*R*,6a*R*)-**6**, -**11**, -**12** (ring-size n=1, 2, 3)[2e] and both diastereomers of **15**[6,7] were prepared according to the literature (Scheme 3).

In the context of the catalytic, enantiocontrolled ethylation of benzaldehyde (Scheme 4),[8] a comparison of the (in β-position epimerized) diastereomeric cyclopentanol derivatives (2*S*,3a*R*,6a*R*)-**6** and (*all-R*)-**6** (*op*-values: 14 and 12%, respectively) does not indicate a generally favoured (2*R*)- or (2*S*)-configuration (Table 1, entries 1 and 4). In addition, the ring-size (n=1, 2 and 3) of the cycloalkanol-subunit and its influence on the catalytic induction process provided by the structures (2*S*,3a*R*,6a*R*)-**6**, -**11** and -**12** is not relevant (*op*-values: 14, 15 and 12%, respectively; entries 1–3).

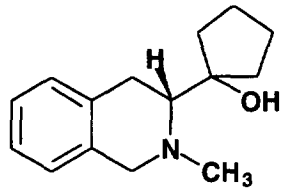
However, the low optical purities were strongly increased up to high *op*-values in the range of 94 to 98% using the *sec*-amino alcohols (*all-R*)-**8**, -**9** and -**10**, in which the rigid cycloalkanol-fragment is replaced by more flexible *n*-alkyl substituents (entries 5–7). Thereby, especially the comparison between compound (*all-R*)-**8** and the corresponding homochiral structure (*all-R*)-**6** with a cyclic 1′,1′-



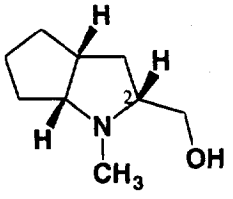
(2*S*,3a*R*,6a*R*)-**6** (n = 1)[2e]
(2*S*,3a*R*,6a*R*)-**11** (n = 2)[2e]
(2*S*,3a*R*,6a*R*)-**12** (n = 3)[2e]



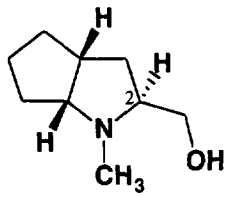
(*S*)-**13**



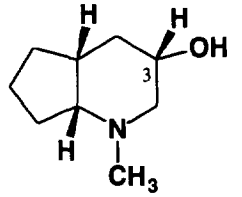
(*R*)-**14**



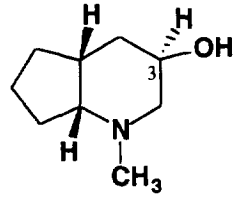
(*all-R*)-**15**[7]



(2*S*,3a*R*,6a*R*)-**15**[6]

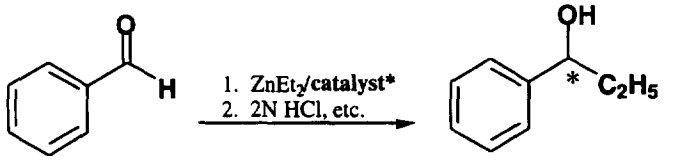


(3*S*,4a*R*,7a*R*)-**16**[6]



(*all-R*)-**16**[6]

Scheme 3.



benzaldehyde 1-phenylpropan-1-ol

Scheme 4. Enantioselective catalytic ethylation of benzaldehyde in the presence of optically active β-amino alcohols **6–16** (the results are summarized in Tables 1 and 2).

bis-substitution is noteworthy: The stereodifferentiating ability of the 1′,1′-*bis*-ethyl compound **8** (entry 5: 98% *op*) is drastically increased compared to the cyclopentanol-structure **6** (entry 4, *op*-value obtained: 12%). With the same number of carbon atoms these two compounds only differ from each other in the additional covalent bond responsible for the ring-closure and the formation of the cycloalkanol-fragment in compound (*all-R*)-**6**. Consequently, differences between (*all-R*)-**6** and (*all-R*)-**8** concerning their inductive efficiency might be attributed to the increased conformative flexibility combined with a higher steric demand of the α-*bis*-ethyl-substitution in compound (*all-R*)-**8**. Here, this seems to be more important for the chiral-catalytic process than the conformative rigidity of the ligand structure.

Apparently a sterically demanding α-*bis*-substitution [see compounds (*all-R*)-**8**, (*all-R*)-**9** and (*all-R*)-**10** with a highly effective (*R*)-induction leading to *op*-values between 94 and 98% *op*] seems to be crucial for the enhancement of the stereocontrol originating from the (*all-R*)-configurated *sec*-amino alcohol structure. This is additionally proved by the result of the excellent inductive capability of (*all-R*)-**1d** (100% *op*).[4c]

In the series of β-amino alcohols with a cycloalkanol subunit an additional *N*-methylation is (referred to the corresponding homochiral *sec*-amino-*tert*-alcohol (*all-R*)-**6** (*op*-value: 12%)) essential to provide a significant increase of the enantioselectivity. This is confirmed by the *N*-methylated β-amino alcohol (*all-R*)-**7** with 99% *op* (Table 2, entry 1). Regarding the modest results (*op* up to 53%;

Table 1. Enantioselective addition of diethylzinc to benzaldehyde in the presence of β-*sec*-amino alcohols; product: 1-phenylpropan-1-ol

Entry	Catalyst*	Ring-size n	Conc. [mol %]	Temp. [°C]	Yield [%]	$[\alpha]_D^{20}$ (*c*)[a]	*op* [%][b]	Config.
1	(2*S*,3a*R*,6a*R*)-**6**	1	10	23	81	+ 6.6 (5.15)	14	*R*
2	(2*S*,3a*R*,6a*R*)-**11**	2	10	21	78	+ 6.8 (5.10)	15	*R*
3	(2*S*,3a*R*,6a*R*)-**12**	3	10	23	78	+ 5.6 (5.21)	12	*R*
4	(*all-R*)-**6**	–	5	23	76	– 5.3 (5.11)	12	*S*
5	(*all-R*)-**8**	–	10	25	71	+ 44.5 (5.18)	98	*R*
6	(*all-R*)-**9**	–	10	22	76	+ 44.4 (5.37)	98	*R*
7	(*all-R*)-**10**	–	10	22	91	+ 42.7 (5.94)	94	*R*

[a] solvent: chloroform; [b] $[\alpha]_D^{20}$ = + 45.45 (*c* = 5.15, $CHCl_3$) for (*R*)-1-phenylpropan-1-ol[9,10].

Table 2. Enantioselective addition of diethylzinc to benzaldehyde in the presence of *N*-methylated β-*tert*-amino alcohols; product: 1-phenylpropan-1-ol

Entry	Catalyst*	Conc. [mol %]	Temp. [°C]	Yield [%]	$[\alpha]_D^{20}$ (*c*)[a]	*op* [%][b]	Config.
1	(*all-R*)-**7**	5	21	71	+ 44.9 (5.41)	99	*R*
2	(*S*)-**13**	5	19	75	– 7.7 (5.12)	17	*S*
3	(*R*)-**14**	5	20	64	– 10.6 (5.12)	23	*S*
4	(*all-R*)-**15**	10	22	97	+ 14.7 (5.09)	32	*R*
5	(2*S*,3a*R*,6a*R*)-**15**	10	22	86	+ 24.1 (5.20)	53	*R*
6	(3*S*,4a*R*,7a*R*)-**16**	10	24	71	– 28.8 (5.22)	64	*S*
7	(*all-R*)-**16**	10	23	69	+ 15.5 (5.09)	34	*R*

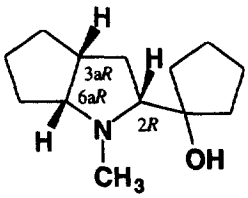
[a] solvent: chloroform; [b] $[\alpha]_D^{20}$ = + 45.45 (*c* = 5.15, $CHCl_3$) for (*R*)-1-phenylpropan-1-ol[9,10].

entries 4 and 5) obtained with the diastereomeric compounds (*all-R*)-**15** and (2*S*,3a*R*,6a*R*)-**15** bearing a primary alcohol function, the positive influence of the bulky cycloalkanol-framework can be seen here. In addition, the ring-expanded isomers (3*S*,4a*R*,7a*R*)-**16** and (*all-R*)-**16** (featuring a secondary alcohol function directly connected with the stereogenic C3-position) give *op*-values of 64 and 34% (entries 6 and 7).

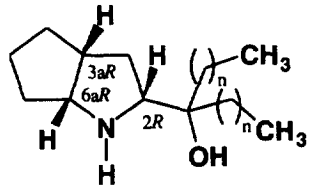
Referred to pyrrolidine-, respectively proline-derivatives with a five-membered, monocyclic backbone, the introduction of a condensed second ring in the derivatives of (*all-R*)-**1a** (further enhancing

the rigidity) positively influences the stereocontrol in the enantioselective ethylation step: compared to the (*S*)-proline derived, bicyclic compound (*S*)-**13** (*op*-value: 17%; entry 2 or (*R*)-**14**: 23% *op*; entry 3) the analogous octahydro-cyclopenta[*b*]pyrrole system (*all-R*)-**7** with a cyclopentanol-subunit leads to a drastically increased enantioselectivity (99% *op*; entry 1). Furthermore, the comparison of the α-*bis*-phenyl structures with a secondary amino function (*S*)-diphenyl(pyrrolidin-2-yl)methanol (24% *op*)[7] and the corresponding octahydro-cyclopenta[*b*]pyrrole system (*all-R*)-**1d** (as mentioned above: 99% *op*)[4c] provide further experimental support for this assumption.

In conclusion, the compilation in Scheme 5 shows the most efficient catalyst-precursors based on the (*all-R*)-octahydro-cyclopenta[*b*]pyrrole-2-carboxylic acid benzyl ester (*all-R*)-**1a**. Noteworthy is the significant influence of the (*all-R*)-framework (building block of *all-R* structures depicted in Scheme 5) as well as the importance of a bulky α-substitution at the hydroxyl function on the inductive efficiency of these auxiliaries.



(*all-R*)-**7**: 99 % *op*



(*all-R*)-**8** (n = 1): 99 % *op*
(*all-R*)-**9** (n = 2): 98 % *op*
(*all-R*)-**10** (n = 3): 94 % *op*

Scheme 5.

These (*R*)-inducing structures are highly efficient, complementary catalysts with regard to several (*S*)-proline-derived catalysts with a favored (*S*)-induction (for example: (*S*)-diphenyl-(1-methylpyrrolidin-2-yl)-methanol).[11]

Experimental section

All reactions were carried out in oven dried glassware under argon atmosphere using anhydrous solvents. Melting points were taken on a melting point apparatus according to Dr Linström and are uncorrected. Optical 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, isobutane). Elemental analyses (C, H, N) were performed on a Carlo Erba Stumentalione (MOD 1104) analyzer. Commercially available chemicals were used. The *N*-Boc-protected amino alcohols, e.g. the starting materials for the synthesis of the new compounds[12] **7–10**, **13** and **14** were prepared according to previously published procedures.[2c,5] Furthermore, structures (*all-R*)-**6**,[2c] (2*S*,3a*R*,6a*R*)-**6**, **-11**, **-12**[2e] and **15–16**[6,7] were also tested in the enantioselective ethylation of benzaldehyde.

General procedure 1

Reduction of various *N*-Boc-protected amino alcohol structures with $LiAlH_4$ affording the corresponding *N*-methylated *tert*-amino alcohols **7**, **13** and **14**:

To a suspension of 1.1 g (29.4 mmol) lithium aluminium hydride in 70 ml THF (stirred for 1 h under reflux then cooled down to room temperature) 3.0 mmol of the respective *N-tert*-butoxycarbonyl derivative (dissolved in 10 ml of THF) are added dropwise within 30 min at room temperature under argon atmosphere. Then the reaction mixture is heated under reflux for 18 h. The heating bath is removed and 5% aqueous KOH is added cautiously at room temperature to destroy the excess reducing reagent. After two additional hours under reflux, the resulting white suspension is filtered, the solids are intensively washed with additional solvent (THF or MTBE) and the combined organic

phases are concentrated *in vacuo* after drying with $MgSO_4$ to afford colourless or slightly yellow oils as crude products. In all cases further purification of the crude products is accomplished by flash-chromatography or Kugelrohr distillation ("bulb-to-bulb" distillation utilizing a Büchi GKR-51 system) under reduced pressure. A more detailed description of the individual work-up is given below under the name of each compound.

(all-R)-(1-tert-Butoxycarbonyl-octahydro-cyclopenta[b]pyrrole-2-yl)-1',1'-diethyl-methanol (all-R)-3

Prepared according to a previously described procedure[2c,5] from 5.38 g (20 mmol) of (*all-R*)-(1-*tert*-butoxycarbonyl)-octahydro-cyclopenta[*b*]pyrrole-2-carboxylic acid methyl ester;[2c,5] work-up: purification by flash-chromatography (silica gel 60, eluents: *n*-hexane/EtOAc 9: 1, TLC: R_f-value: 0.46); yield: 3.9 g (66%), product: colourless oil; $[\alpha]^{20}_D$=+1.9 (*c*=0.94, CH_2Cl_2); IR (NaCl): ν=3610–3200 cm^{-1} (OH), 1690–1650 (-C=O); ^{1}H-NMR ($CDCl_3$): δ=0.84–0.99 (q, *J*=9.2 Hz, 6H, 2×CH_2CH_3), 1.06–1.96 (3m, 11H, H3a, 2×H4, 2×H5, 2×H6, 2×CH_2CH_3), 1.44 (s, 9H, $OC(CH_3)_3$), 2.05–2.20 (m, 1H, 1×H3), 2.43–2.57 (m, 1H, 1×H3), 3.89–3.97 (m, 1H, H6a), 4.11–4.24 (m, 1H, H2), 6.52 (s, 1H, COH); ^{13}C-NMR ($CDCl_3$): δ=7.44 (2C, 2×CH_2CH_3), 28.38 (3C, $OC(CH_3)_3$), 23.56, 26.75 (2C, 2×CH_2CH_3), 29.42, 30.61, 32.77, 34.92 (4C, C3, C4, C5, C6), 39.65 (1C, C3a), 65.96, 69.05 (2C, C6a, C2), 74.19 (1C, COH), 80.23 (1C, $OC(CH_3)_3$), 158.23 (1C, R_2NCO_2R); MS (CI, *i*-butane): 298 (MH^+, 100%); Anal. calc. for $C_{17}H_{31}NO_3$ (297.2): C, 68.63; H, 10.51; N, 4.71; found: C, 68.57; H, 10.47; N, 4.74.

(all-R)-(1-tert-Butoxycarbonyl-octahydro-cyclopenta[b]pyrrole-2-yl)-1',1'-dipropyl-methanol (all-R)-4

Prepared according to a previously described procedure[2c,5] from 2.69 g (10 mmol) of (*all-R*)-(1-*tert*-butoxycarbonyl)-octahydro-cyclopenta[*b*]pyrrole-2-carboxylic acid methyl ester;[2c,5] work-up: purification by flash-chromatography (silica gel 60, eluents: *n*-hexane/EtOAc 8: 2, TLC: R_f-value: 0.73); yield: 1.3 g (40%), product: colourless oil; $[\alpha]^{20}_D$=+20.3 (*c*=0.79, $CHCl_3$); IR (NaCl): ν=3320 cm^{-1} (OH), 1655 (-C=O); ^{1}H-NMR ($CDCl_3$): δ=0.85–0.94 (m, 6H, 2×$CH_2CH_2CH_3$), 1.25–1.95 (m, 15H, 2×$CH_2CH_2CH_3$, H3a, 2×H4, 2×H5, 2×H6), 1.47 (s, 9H, $OC(CH_3)_3$), 2.17 (m, 1H, 1×H3), 2.56 (m, 1H, 1×H3), 3.93 (dd, *J*=7.14 Hz, *J*=11.12 Hz, 1H, H2), 4.14–4.22 (m, 1H, H6a), 6.52 (s, 1H, OH); ^{13}C-NMR ($CDCl_3$): δ=14.82, 15.16 (2C, 2×$CH_2CH_2CH_3$), 16.11, 16.25 (2C, 2×$CH_2CH_2CH_3$), 28.37 (3C, $OC(CH_3)_3$), 23.62, 30.58, 32.77, 35.06, 37.18, 40.44 (6C, 2×$CH_2CH_2CH_3$, C3, C4, C5, C6), 39.69 (1C, C3a), 66.01, 69.55 (2C, C2, C6a), 74.42 (1C, COH), 80.23 (1C, $OC(CH_3)_3$), 157.76 (1C, R_2NCO_2R); MS (CI, *i*-butane): 326 (MH^+, 100%); Anal. calc. for $C_{19}H_{35}NO_3$ (325.6): C, 70.08; H, 10.83; N, 4.30; found: C, 70.12; H, 10.80; N, 4.37.

(all-R)-(1-tert-Butoxycarbonyl-octahydro-cyclopenta[b]pyrrole-2-yl)-1',1'-dibutyl-methanol (all-R)-5

Prepared according to a previously described procedure[2c,5] from 2.69 g (10 mmol) of (*all-R*)-(1-*tert*-butoxycarbonyl)-octahydro-cyclopenta[*b*]pyrrole-2-carboxylic acid methyl ester;[2c,5] work-up: purification by chromatography (silica gel 60, eluents: *n*-hexane/ethyl acetate 4:1, TLC: R_f-value: 0.75); product: colourless oil; yield: 1.31 g (37%); $[\alpha]^{20}_D$=+20.0 (*c*=1.17, $CHCl_3$); IR (NaCl): ν=3350 cm^{-1} (OH), 1670 (-C=O); ^{1}H-NMR ($CDCl_3$): δ=0.89 (t, *J*=7.5 Hz, 6H, 2×CH_2CH_3), 1.13–1.97 (m, 19H, H3a, 2×H4, 2×H5, 2×H6, 2×$(CH_2)_3CH_3$), 1.45 (s, 9H, $OC(CH_3)_3$), 2.08–2.17 (m, 1H, 1×H3), 2.43–2.56 (m, 1H, 1×H3), 3.92 (dd, *J*=7.2 Hz, *J*=11.2 Hz, 1H, H2), 4.13–4.21 (m, 1H, H6a), 6.49–6.60 (m, 1H, OH); ^{13}C-NMR ($CDCl_3$): δ=14.04, 14.09 (2C, 2×CH_2CH_3), 23.57, 23.74, 25.14, 30.58, 32.78, 34.40, 35.03, 37.83 (16C, C3, C4, C5, C6, 2×$(CH_2)_3CH_3$), 28.36 ($OC(CH_3)_3$), 39.71 (1C, C3a), 65.98, 69.55 (2C, C6a, C2), 74.31 (1C, COH), 80.20 ($OC(CH_3)_3$), 157.71 (C=O); MS (CI, *i*-butane): 354 (MH^+, 100%); Anal. calc. for $C_{21}H_{39}NO_3$ (353.6): C, 71.34; H, 11.12; N, 3.96; found: C, 71.33; H, 11.19; N, 3.94.

(all-R)-1′-(1-Methyl-octahydro-cyclopenta[b]pyrrole-2-yl)cyclopentanol (all-R)-7

Prepared according to general procedure 1 from 0.71 g (2.4 mmol) of *(all-R)*-1′-(1-*tert*-butoxycarbonyl-octahydro-cyclopenta[*b*]pyrrole-2-yl)cyclopentanol *(all-R)*-**2**;[2c,5] work-up: purification by flash-chromatography (silica gel 60, eluents: *n*-hexane/EtOAc 8: 2, addition of 20 ml triethylamine per liter of the solvent mixture, TLC: R_f-value: 0.63); yield: 0.40 g (80%), product: colourless oil, slow crystallization in the fridge at +4°C; $[\alpha]^{20}_D$=+40.5 (*c*=0.22, CH_2Cl_2); IR (NaCl): ν=3620–3160 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$): δ=1.20–1.94 (4m, 16H, 4×cyclopentyl-CH_2, H3a, 2×H4, 2×H5, 2×H6, NH), 1.96–2.09 (m, 1H, 1×H3), 2.18–2.49 (m, 1H, H6a), 2.33 (s, 3H, NCH_3), 2.94–3.05 (m, 1H, H2), 3.68 (s, 1H, COH); ^{13}C-NMR ($CDCl_3$): δ=23.08, 23.87, 24.71, 33.13, 33.57, 35.69, 38.60, 39.40, 41.20, 41.50 (10C, 4×cyclopentyl-CH_2, C3, C4, C5, C6, C3a, NCH_3), 73.98, 74.99 (2C, C6a, C2), 79.93 (1C, COH); MS (CI, *i*-butane): 210 (MH^+, 100%); Anal. calc. for $C_{13}H_{23}NO$ (209.2): C, 74.5; H, 11.08; N, 6.69; found: C, 74.51; H, 11.02; N, 6.68.

(all-R)-1′,1′-Diethyl-(octahydro-cyclopenta[b]pyrrole-2-yl)methanol (all-R)-8

Prepared according to a previously described procedure[2c,5] from 0.8 g (2.7 mmol) of *(all-R)*-(1-*tert*-butoxycarbonyl-octahydro-cyclopenta[*b*]pyrrole-2-yl)-1′,1′-diethyl-methanol *(all-R)*-**3**; work-up: shortway distillation ("bulb-to-bulb" distillation using a Büchi-GKR-51 system) at temperatures between 140–180°C (0.04 mbar), product: colourless solid; yield: 0.42 g (79%), product: colourless oil; m.p.: 47°C; IR (KBr): ν=3600–3160 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$): δ=0.77–0.91 (m, 6H, 2×CH_2CH_3), 1.24–1.69 (m, 12H, H3a, 2×H4, 2×H5, 2×H6, NH, 2×CH_2CH_3), 1.80–1.94 (m, 1H, 1×H3), 2.46–2.61 (m, 1H, 1×H3), 3.03–3.16 (m, 1H, H6a), 3.65–3.77 (m, 1H, H2); ^{13}C-NMR ($CDCl_3$): δ=7.66, 7.97 (2C, 2×CH_2CH_3), 23.45, 26.94 (2C, 2×CH_2CH_3), 29.57, 32.70, 33.07, 35.09 (4C, C3, C4, C5, C6), 41.59 (1C, C3a), 62.13, 64.23 (2C, C6a, C2), 72.82 (1C, COH); MS (CI, *i*-butane): 198 (MH^+, 100%); Anal. calc. for $C_{12}H_{23}NO$ (197.2): C, 73.03; H, 11.76; N, 7.10; found: C, 73.00; H, 11.80; N, 7.03.

(all-R)-1′,1′-Dipropyl-(octahydro-cyclopenta[b]pyrrole-2-yl)methanol (all-R)-9

Prepared according to a previously described procedure[2c,5] from 0.9 g (2.7 mmol) of *(all-R)*-(1-*tert*-butoxycarbonyl-octahydro-cyclopenta[*b*]pyrrole-2-yl)-1′,1′-dipropyl-methanol *(all-R)*-**4**; product: yellow oil; yield: 0.52 g (83%); $[\alpha]^{20}_D$=+33.6 (*c*=1.32, $CHCl_3$); IR (NaCl): ν=3500–3200 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$): δ=0.85–0.91 (m, 6H, 2×$CH_2CH_2CH_3$), 1.18–1.68 (m, 16 H, 2×$CH_2CH_2CH_3$, H3a, 2×H4, 2×H5, 2×H6, NH), 1.77–1.87 (m, 1H, 1×H3), 2.59–2.45 (m, 1H, 1×H3), 3.03 (dd, *J*=5.73 Hz, *J*=10.65 Hz, 1H, H2), 3.65–3.72 (m, 1H, H6a); ^{13}C-NMR ($CDCl_3$): δ=14.73, 14.77 (2C, 2×$CH_2CH_2CH_3$), 16.62, 16.95 (2C, 2×$CH_2CH_2CH_3$), 23.46, 32.77, 33.05, 35.19, 37.69, 40.60 (8C, 2×$CH_2CH_2CH_3$, C3, C4, C5, C6), 41.61 (1C, C3a), 62.09, 64.87 (2C, C2, C6a), 72.44 (1C, COH); MS (CI, *i*-butane): 226 (MH^+, 100%); Anal. calc. for $C_{14}H_{27}NO$ (225.4): C, 74.60; H, 12.07; N, 6.21; found: C, 74.48; H, 12.01; N, 6.22.

(all-R)-1′,1′-Dibutyl-(octahydro-cyclopenta[b]pyrrole-2-yl)methanol (all-R)-10

Prepared according to a previously described procedure[2c,5] from 1.06 g (3 mmol) of *(all-R)*-1′,1′-Dibutyl-(1-*tert*-butoxycarbonyl-octahydro-cyclopenta[*b*]pyrrole-2-yl)methanol *(all-R)*-**5**; yield: 0.48 g (63%), product: colourless oil; $[\alpha]^{20}_D$=+33.2 (*c*=1.8, $CHCl_3$); IR (NaCl): ν=3500–3200 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$): δ=0.88 (t, *J*=7.1 Hz, 6H, 2×CH_2CH_3), 1.06–1.72 (m, 19H, H3a, 2×H4, 2×H5, 2×H6, 2×$(CH_2)_3CH_3$), 1.78–1.86 (m, 1H, 1×H3), 2.44–2.56 (m, 1H, 1×H3), 3.02 (dd, *J*=5.7 Hz, *J*=10.6 Hz, 1H, H2); 3.64–3.69 (m, 1H, H6a); ^{13}C-NMR ($CDCl_3$): δ=13.95, 14.03 (2C, 2×CH_2CH_3), 23.37, 23.45, 25.49, 25.85, 32.76, 33.04, 34.94, 35.20, 37.85 (16C, C3, C4, C5, C6, 2×$(CH_2)_3CH_3$), 41.61 (1C, C3a), 62.06, 64.86 (2C, C6a, C2), 72.39 (1C, COH); MS (CI, *i*-butane): 254 (MH^+, 100%); Anal. calc. for $C_{16}H_{31}NO$ (253.5): C, 75.81; H, 12.33; N, 5.52; found: C, 75.80; H, 12.28; N, 5.55.

*(S)-1′-(1-Methyl-pyrrolidin-2-yl)cyclopentanol (S)-**13***

Prepared according to general procedure 1 from 0.70 g (2.74 mmol) of (*S*)-1′-(1-*tert*-butoxycarbonyl-pyrrolidin-2-yl)cyclopentanol;[2c,5] work-up: purification by flash-chromatography (silica gel 60, eluents: *n*-hexane/ triethylamine 8.5: 1.5, TLC: R_f-value: 0.54); yield: 0.38 g, (82%), product: colourless oil; $[\alpha]^{20}_D = -49.9$ (c=0.53, CH_2Cl_2); IR (NaCl): ν=3680–3210 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$): δ=1.20–1.91 (2m, 12H, 4×cyclopentyl-CH_2, 2×H3, 2×H4), 2.26–2.38 (m, 2H, 2×H5), 2.44 (s, 3H, NCH_3), 3.00–3.09 (m, 1H, H2), 3.17 (s, 1H, COH); ^{13}C-NMR ($CDCl_3$): δ=23.10, 24.33, 24.37, 28.55, 36.97, 40.61, 43.35 (7C, 4×cyclopentyl-CH_2, C3, C4, NCH_3), 58.67 (1C, C5), 73.03 (1C, C2), 82.41 (1C, COH); MS (CI, *i*-butane): 170 (MH^+, 100%); Anal. calc. for $C_{10}H_{19}NO$ (169.2): C, 70.94; H, 11.32; N, 8.28; found: C, 70.88; H, 11.34; N, 8.25.

*(R)-(2-Methyl-1,2,3,4-tetrahydro-isochinolin-3-yl)cyclopentanol (R)-**14***

Prepared according to general procedure 1 from 0.64 g (2.0 mmol) of (*R*)-1′-(2-*tert*-butoxycarbonyl-1,2,3,4-tetrahydroisochinolin-3-yl)cyclopentanol;[2c,5] yield: 0.40 g (87%), product: colourless oil; $[\alpha]^{20}_D = -25.8$ (c=1.26, CH_2Cl_2); IR (NaCl): ν=3620–3100 cm^{-1} (OH); ^{1}H-NMR (300 MHz, $CDCl_3$): δ=1.62–1.94 (m, 8H, 4×cyclopentyl-CH_2), 2.36 (s, 3H, NCH_3), 2.66–2.91 (m, 3H, 2×H4, H3), 3.74 (d, J=15.4 Hz, 1H, 1×H1), 3.92 (d, J=15.4 Hz, 1H, 1×H1), 7.02–7.25 (m, 4H, aromat.-H); ^{13}C-NMR ($CDCl_3$): δ=23.34, 24.12, 26.24, 35.33 (4C, 4×cyclopentyl-CH_2), 39.88 (1C, C4), 43.55 (1C, C3), 55.44 (1C, NCH_3), 66.16 (1C, C1), 83.21 (1C, COH), 125.88, 126.58, 126.70, 127.78 (4C, aromat.-C), 135.21, 135.76 (2C, q. aromat.-C); MS (CI, *i*-butane): *m/z* (%)=232 (MH^+, 100%); Anal. calc. for $C_{15}H_{21}NO$ (231.2): C, 77.87; H, 9.16; N, 6.06; found: C, 77.7; H, 9.16; N, 6.03.

General procedure 2

Enantiocontrolled addition of diethylzinc to benzaldehyde in the presence of catalytic amounts of amino alcohols **6–16** generally based on the octahydro-cyclopenta[*b*]pyrrole system (the results are summarized in Tables 1 and 2).

Under argon atmosphere a solution of 0.5 mmol of the respective catalyst precursor (alternatively 0.2 or 1 mmol, e.g. utilizing 2, 5 or 10 mol% of amino alcohols **2–14**) in 20 ml of anhydrous toluene is prepared. After cooling to −40°C (with ethanol/liquid nitrogen) 18.2 ml (20 mmol) of a 1.1 M diethylzinc solution in toluene are added within 10 minutes. After 30 minutes with stirring at constant temperature the clear solution is allowed to warm to room temperature. Then 1.06 g (10 mmol) freshly distilled benzaldehyde, dissolved in 20 ml of anhydrous toluene, are added over a 30-min period. The mixture is stirred for an additional 40 h (at least 16 h) and quenched at 0°C by the addition of 60 ml 2 N aqueous HCl. After separation of the layers the water phase is extracted with diethyl ether (3×40 ml) and the combined organic extracts are subsequently washed with 3.9% $NaHSO_3$-solution (3×40 mL), saturated aqueous $NaHCO_3$-solution and finally with brine. After drying with $MgSO_4$ solvents are removed under reduced pressure and the residual oil is purified by distillation *in vacuo* (chemical yields: between 64 and 86%). The optical purity[10] is determined by optical rotation analysis: $[\alpha]^{20}_D = +45.45$ (c=5.15, $CHCl_3$) for (*R*)-1-phenylpropan-1-ol.[9]

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