Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 4437–4445

TETRAHEDRON: *ASYMMETRY*

Synthesis and application of C_2-symmetrical bis-β-amino alcohols based on the octahydro-cyclopenta[*b*]pyrrole system in the catalytic enantioselective addition of diethylzinc to benzaldehyde

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Received 21 October 1999; accepted 25 October 1999

Abstract

Asymmetric catalytic ethylation of benzaldehyde utilizing a series of new, tetradental bis-β-amino alcohols based on the octahydro-cyclopenta[*b*]pyrrole system — derived from an industrial waste material — is presented. Attention is focused on steric aspects of the catalyst(-precursor) structure. Furthermore, the catalytic efficiency of the ethylene-bridged, C_2-symmetrical bis-β-amino alcohols is compared to related 'monomeric' structures. Potent chiral ligands, which are highly effective even at concentrations of below 2 mol%, have been developed reaching excellent enantioselectivities up to 100% *ee*.

1. Introduction

In the context with our on-going studies on the utilization of industrial waste materials, we used (*all-R*)-**1**[1] in the synthesis of new cost-effective enantioselective catalysts that exhibit high reactivity and enantioselectivity and which are suitably designed for various applications. Ligands derived from the proline analogous octahydro-cyclopenta[*b*]pyrrole system have been successfully applied in a variety of asymmetric transformations, among them the enantiocontrolled catalytic diethylzinc addition to aldehydes (best result reached so far: 100% *ee* at 10 mol% catalyst concentration),[2] the enantioselective oxazaborolidine-catalyzed reduction of ketones (best result: 91% *o.p.*),[3] the ruthenium-catalyzed transfer hydrogenation (86% *ee*)[4] and the palladium-induced enantioselective protonation reaction (72% *ee*).[5]

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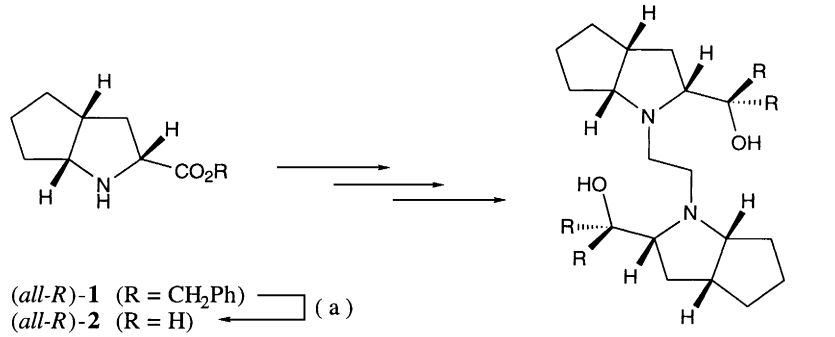
0957-4166/99/$ - see front matter
PII: S0957-4166(99)00475-9

These positive results inspired us to search for even more powerful calalysts based on (*all-R*)-**1** for the enantioselective ethylation reaction.

Some of our previously published efforts have focused on the evaluation of structural features governing the extent of the chiral induction generated by β-amino alcohols: based on the bicyclic backbone, which provides a limited flexibility and beneficial steric factors, the correlation of up to four internal stereogenic centers, the variation of the α-substitution, the *N*-methylation and the ring-size of an additional cycloalkanol subunit in the ligand structure were tested.[2d,e] In this paper, the study is extended to tetradental, C_2-symmetrical bis-β-amino alcohols. As a result, a new structure, (*all-R*)-**5**, is one of the most efficient ligands which has been developed to date for the enantioselective alkylation of benzaldehyde by diethylzinc (Scheme 1).[6]



Scheme 1. (a) Cyclohexene/Pd/C in MeOH/H_2O[7]

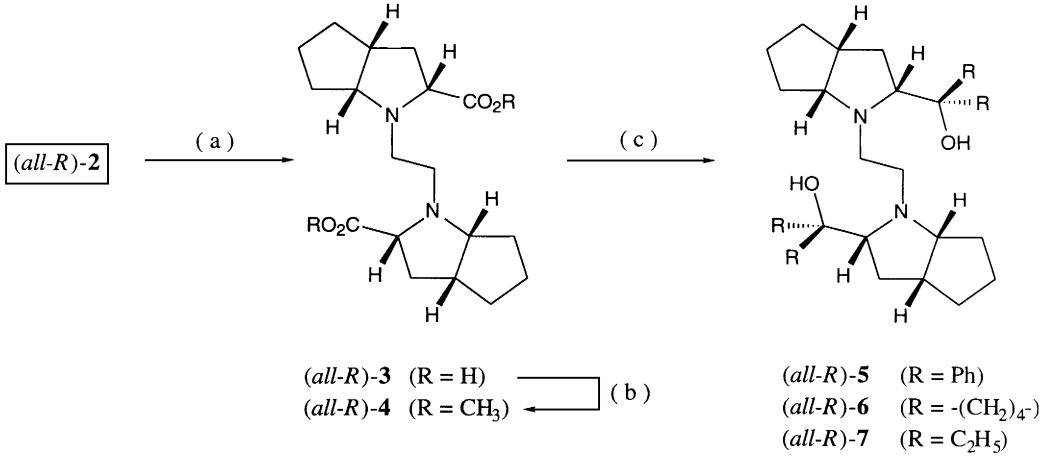
2. Results and discussion

Sterically constrained tetradental ligands bearing two β-amino alcohol subunits are prepared starting from the amino acid (*all-R*)-**2** — obtained after recrystallization and hydrogenolytic cleavage of the benzyl ester function of (*all-R*)-**1**[1] — by dimerization via 1,2-dibromoethane/K_2CO_3 in 4.5 M aqueous NaOH[7] followed by esterification with $SOCl_2$/MeOH (Scheme 2). The resulting diester intermediate (*all-R*)-**4** reacted with Grignard reagents yielding the ethylene-bridged structures (*all-R*)-**5**–**7** containing a double *tert*-amino–*tert*-alcohol framework. The product isolation is performed by flash chromatography on silica gel (yield: 23–42%).

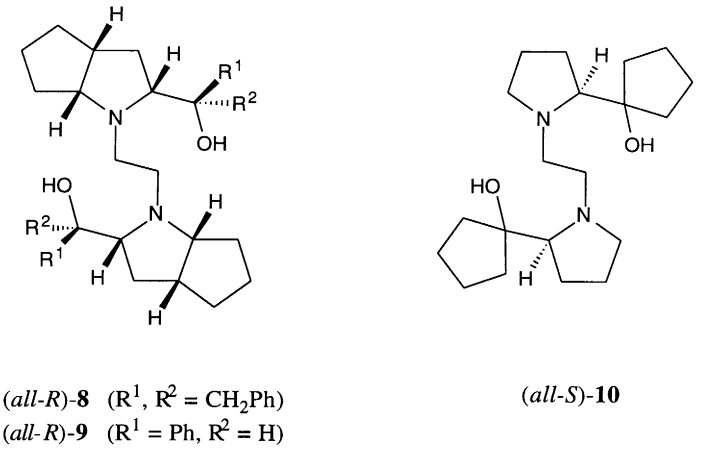
A different approach had to be used for the synthesis of related structures (*all-R*)-**8**, (*all-R*)-**9** and (*all-S*)-**10** (Scheme 3). These compounds were obtained starting from corresponding, previously described[7] *sec*-amino alcohols by coupling of two amine units via 1,2-dibromoethane/K_2CO_3 in acetonitrile. Further details are given in the Experimental section.

According to a typical procedure, catalysts **5**–**10** and related ligands **11**–**14** were tested in the enantioselective addition of diethylzinc to the model substrate benzaldehyde at room temperature (see Scheme 4). The results are given in Table 1. These results show that the (*R*)-enantiomer of 1-phenylpropan-1-ol is preferentially obtained with (*all-R*)-**1** derived catalysts in 29–82% yield and enantiomeric excesses varying from 7 to 100%.

A comparison of structures **6**, **8** or **9** to related 'monomeric' β-amino alcohols with a secondary or tertiary amino function (R=H or CH_3) does not indicate a generally favored C_2 symmetry for the inductive efficiency (for example, see the bis-amino alcohols in comparison with the corresponding *N*-methylated



Scheme 2. Synthesis of ligands **5**–**7** starting from (*all-R*)-**2**: (a) dibromoethane, K_2CO_3, 4.5 M aq. NaOH; (b) $SOCl_2$, MeOH, 2.1 equiv. Et_3N; (c) Grignard-reaction (PhMgBr, $BrMg(CH_2)_4MgB$ EtMgBr), aq. NH_4Cl, chromatographic separation



Scheme 3. New, tetradental bis-β-amino alcohols **8**–**10** based on (*all-R*)-**2** and (*S*)-proline

structures: **8** and **11**[7] (R^1, R^2=CH_2Ph), **9** and **12**[2e] (R^1=Ph, R^2=H) or **6** and **13**[2d] (R^1, R^2=-$(CH_2)_4$-); the individual results are **8** vs. **11**: 54:90%; **9** vs. **12**: 65:68% and **6** vs. **13**: 90:99% *ee*) (Scheme 5).

Only the already highly effective ligand **14**[2a] is further improved by the dimerization via the ethylene bridge in structure **5**: with a catalyst concentration of 5 mol%, an enantiomeric excess of 99% for **14** (Table 1, entry 10) and 100% for **5** (entry 9) is obtained. At a lower concentration of 1 mol% the superiority of ligand **5** becomes more obvious: the results are 45% (**14**, entry 13) and 88% *ee* (**5**, entry 12). Even at a catalyst concentration of 2 mol% the enantiomeric excess obtained with **5** (entry 11) is still 100%.

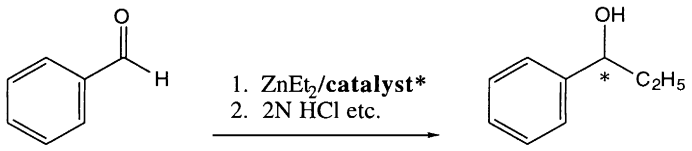
Noteworthy is the significantly increased yield of 1-phenylpropan-1-ol from 29% (obtained with **14**, entry 10) to 73 and 82% (**5**, entries 9 and 12), respectively.

Neither an additional, fourth stereogenic center resulting in a secondary alcohol group (and a favored (*all-R*)-configuration[2e]) in ligand **9** (65% *ee*) nor a decreased conformational flexibility introduced by the rigid cyclopentanol subunit in compound **6** (90% *ee*) improves — compared to the corresponding ligands **5** and **7** (100 and 91% *ee*), respectively — the stereodifferentiating properties originating from the

Table 1
Enantioselective addition of diethylzinc to benzaldehyde in the presence of bis-β-amino alcohols **5**–**10** and β-amino alcohols **11**–**14**; product: 1-phenylpropanol-1-ol

Entry	Catalyst*	Substituents R in α-position	Cat. conc. [mol %]	Temp. [°C]	Yield [%]	*e.e.*[a] [%]	Config.
1	(*all-R*)-**8**	Benzyl	5	22	51	**54**	*R*
2	(*all-R*)-**11**	Benzyl	10	21	40	**90**	*R*
3	(*all-R*)-**9**	H and Phenyl	5	22	47	**65**	*R*
4	(*all-R*)-**9**	H and Phenyl	2	21	59	**69**	*R*
5	(*all-R*)-**12**	H and Phenyl	5	24	64	**68**	*R*
6	(*all-R*)-**6**	$-(CH_2)_4-$	5	21	76	**90**	*R*
7	(*all-R*)-**6**	$-(CH_2)_4-$	2	23	57	**47**	*R*
8	(*all-R*)-**13**	$-(CH_2)_4-$	5	21	71	**99**	*R*
9	(*all-R*)-**5**	Phenyl	5	23	73	**100**	*R*
10	(*all-R*)-**14**	Phenyl	5	20	29	**99**	*R*
11	(*all-R*)-**5**	Phenyl	2	21	73	**100**	*R*
12	(*all-R*)-**5**	Phenyl	1	24	82	**88**	*R*
13	(*all-R*)-**14**	Phenyl	1	20	67	**45**	*R*
14	(*all-R*)-**7**	Ethyl	5	22	68	**91**	*R*
15	(*all-R*)-**7**	Ethyl	2	22	60	**71**	*R*
16	(*all-S*)-**10**	$-(CH_2)_4-$	5	22	79	**41**	*S*
17	(*all-S*)-**10**	$-(CH_2)_4-$	2	21	53	**7**	*S*

[a] enantiomeric excess *e.e.* (%), determined by gas chromatography (GC) performed on a Shimadzu GC-15a instrument (25 m chiral column: SGE Cydex-B, ω_i = 0.25 mm, film thickness: 0.25 μm, 1 μl product in *n*-hexane, detection: FID, carrier gas: nitrogen).

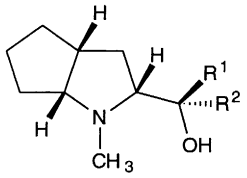


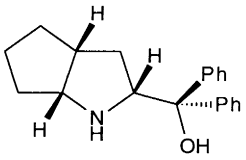
benzaldehyde 1-phenylpropan-1-ol

Scheme 4. Enantioselective catalytic ethylation of benzaldehyde in the presence of optically active ligands **5**–**10** (the results are given in Table 1)

bicyclic (2*R*,3a*R*,6a*R*)-fragment. Thus, a flexible, sterically demanding α-bis-substitution at the hydroxyl function seems to be crucial for the enhancement of the stereocontrol.

The condensed, second ring in the octahydro-cyclopenta[*b*]pyrrole system — further enhancing the rigidity — positively influences the stereocontrol in the enantioselective ethylation step: compared to the (*S*)-proline derived compound (*all-S*)-**10** (*ee* values: 41 and 7%; entries 16 and 17), the analogous (*all-*





(*all-R*)-**11** (R^1, R^2 = CH_2Ph)[7]
(*all-R*)-**12** (R^1 = Ph, R^2 = H)[2e]
(*all-R*)-**13** (R^1, R^2 = -$(CH_2)_4$-)[2d]

(*all-R*)-**14**[2a]

Scheme 5. Catalyst precursors **11**–**14**

R)-**2** derived system (*all-R*)-**6** leads to a drastically increased enantioselectivity (90 and 47% *ee*, entries 6 and 7).

In conclusion, (*all-R*)-**5** is the most efficient catalyst-precursor derived from (*all-R*)-octahydro-cyclopenta[*b*]pyrrole-2-carboxylic acid benzyl ester (*all-R*)-**1** which has been developed so far for the ethylation of benzaldehyde by diethylzinc. Even at concentrations of 2 mol% 1-phenylpropan-1-ol is obtained with 100% *ee* in good chemical yields. Furthermore, compound **5** is another example of the extraordinary enhancement of stereoselectivity in asymmetric synthesis by the non-stereogenic diarylhydroxy-methyl subunit.[8]

3. Experimental

All reactions were carried out in oven dried glassware under argon atmosphere using anhydrous solvents. Thin layer chromatography was carried out on silica gel (60 F_{254}, Merck) and spots located with UV light or iodine vapors. 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 registered 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. Gas chromatography (GC) was conducted on a Shimadzu GC-15a equipped with a 25 m chiral column (SGE Cydex-B, ω_i=0.25 mm, film thickness: 0.25 μm, 1 μl product in *n*-hexane, detection: FID, carrier gas: nitrogen). The starting material (*all-R*)-octahydro-cyclopenta[*b*]pyrrole-2-carboxylic acid benzyl ester (*all-R*)-**1** was obtained from Hoechst AG. Commercially available chemicals were used.

The starting materials for the synthesis of compounds **8**–**10** were prepared according to previously published procedures. Furthermore, structures (*all-R*)-**11**,[7] (α*R*,β*R*)-**12**,[2e] (*all-R*)-**13**[2d] and (*all-S*)-**14**[2a] were also tested in the enantioselective ethylation of benzaldehyde.

*3.1. (*all-R*)-1,2-Bis(methyloctahydro-cyclopenta[*b*]pyrrol-1-yl-2-carboxylate)ethane (*all-R*)-4*

To a solution of (*all-R*)-**3**[7] (20.0 g, 59.5 mmol) in methanol (150 ml), thionyl chloride (21.2 g, 178.4 mmol) is added at 0–5°C. Stirring is continued for 2 h at 0°C and 48 h at room temperature. The solvent is removed under reduced pressure and the residue is recrystallized twice from methanol. The dihydrochloride intermediate (21.3 g, 47.5 mmol) is suspended in dichloromethane (150 ml) and triethylamine (10.1 g, 100 mmol) is added with stirring at room temp. After addition of diethyl ether

(30 ml), triethylamine hydrochloride is removed by filtration. The filtrate is washed with water and dried with $MgSO_4$. Evaporation of the solvent under reduced pressure gives the pure title compound. Yield: 16.9 g (78%); $[\alpha]_D^{20}$=+111.2 (*c* 1.56, CH_2Cl_2); IR (NaCl): ν=1740 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 300 MHz): δ=1.15–1.28, 1.42–1.55, 1.64–1.75 (3m, 14H, 2×H4′, 2×H4′′, 2×H5′, 2×H5′′, 2×H6′, 2×H6′′, H3a′, H3a′′), 2.13–2.26 (m, 2H, H3′, H3′′), 2.51–2.67 (m, 4H, 2×H1, 2×H2), 2.67–2.85 (m, 2H, H3′, H3′′), 3.04–3.09 (m, 2H, H6a′, H6a′′), 3.16–3.27 (m, 2H, H2′, H2′′), 3.15 (s, 6H, 2×OCH_3); ^{13}C NMR ($CDCl_3$): δ=24.2, 32.6, 34.4, 37.1 (C3′, C3′′, C4′, C4′′, C5′, C5′′, C6′, C6′′), 41.6 (C3a′, C3a′′), 51.7 (C1, C2), 53.2 (2×O*C*H_3), 68.4, 70.7 (C2′, C2′′, C6a′, C6a′′), 174.1 (2×C=O); MS (CI, *i*-butane): *m/z* (%)=365 (100) [MH^+]; anal. calcd for $C_{20}H_{32}N_2O_2$ (364.4): C, 65.89; H, 8.85; N, 7.69; found: C, 65.81; H, 8.43; N, 7.44.

3.2. (all-R)-1,2-Bis[2-(diphenyl-methanol-yl)octahydro-cyclopenta[b]pyrrol-1-yl]ethane (all-R)-**5**

To a freshly prepared Grignard-solution consisting of bromobenzene (31.1 g, 198.2 mmol) and magnesium (4.8 g, 198.2 mmol) in dry THF (350 ml), (*all-R*)-**4** (4.5 g, 124 mmol; dissolved in 100 ml of dry THF) is added dropwise at 0–5°C within 1.5 h under argon atmosphere. The reaction mixture is kept at room temperature for 80 h and the reaction is then quenched by the addition of a sat. aqueous NH_4Cl-solution (250 ml). After phase separation and extraction of the aqueous layer with toluene (40 ml), the combined organic phases are dried with $MgSO_4$ and finally concentrated in vacuo. The resulting yellow solid is recrystallized from dichloromethane/methanol. Yield (not optimized): 1.73 g (23%); mp: 238–239°C; $[\alpha]_D^{20}$=+70.7 (*c* 1.01, CH_2Cl_2); IR (NaCl): ν=3260 cm^{-1} (OH); ^1H NMR ($CDCl_3$, 300 MHz): δ=1.04–1.77 (4m, 16H, H3′, H3′′, 2×H4′, 2×H4′′, 2×H5′, 2×H5′′, 2×H6′, 2×H6′′, H3a′, H3a′′), 1.91–2.10 (2m, 4H, 2×H1, 2×H2), 2.19–2.25 (m, 2H, H3′, H3′′), 2.44–2.53 (m, 2H, H6a′, H6a′′), 3.83 (d, *J*=14 Hz, 2H, H2′, H2′′), 4.95–5.15 (s, 2H, 2×O*H*), 7.05–7.75 (m, 20H, aromat.-H); ^{13}C NMR ($CDCl_3$): δ=23.8, 32.1, 35.1, 35.9 (C3′, C3′′, C4′, C4′′, C5′, C5′′, C6′, C6′′), 39.9 (C3a′, C3a′′), 51.1 (C1, C2), 70.6, 72.0 (C2′, C2′′, C6a′, C6a′′), 74.8 (2×*C*OH), 125.1, 125.3, 126.0, 126.1, 127.8, 128.2 (2×6 aromat.-C), 147.1, 148.9 (2×2 q. aromat.-C); MS (CI, *i*-butane): *m/z* (%)=613 (100) [MH^+]; anal. calcd for $C_{42}H_{48}N_2O_2$ (612.1): C, 82.31; H, 7.89; N, 4.57; found: C, 81.59; H, 7.96; N, 4.12.

3.3. (all-R)-1,2-Bis[2-(cyclopentan-1-ol-1-yl)octahydro-cyclopenta[b]pyrrol-1-yl]ethane (all-R)-**6**

To a Grignard-solution consisting of 1,4-dibromobutane (11.1 g, 51.4 mmol) and magnesium (2.5, 102.7 mmol) in dry THF (500 ml), (*all-R*)-**4** (2.3 g, 6.4 mmol; dissolved in 250 ml of dry THF) is added dropwise at –5 to 0°C within 2 h. The reaction mixture is then kept at room temperature for 80 h and hydrolyzed with sat. aqueous NH_4Cl-solution. After phase separation and extraction of the aqueous layer with toluene (40 ml), the combined organic phases are dried with $MgSO_4$ and concentrated in vacuo. The resulting brown crude oil is purified by column chromatography (silica gel 60, eluents: *n*-hexane:triethylamine 9:1, TLC: R_f-value: 0.90). Further purification was performed by recrystallization from ethanol/diethyl ether. Yield (not optimized): 1.09 g (41%); mp: 83°C; $[\alpha]_D^{20}$=+59.3 (*c* 1.00, CH_2Cl_2); IR (NaCl): ν=3320–3440 cm^{-1} (OH); ^1H NMR ($CDCl_3$, 300 MHz): δ=1.29–2.01 (m, 32H, H3′, H3′′, 2×H4′, 2×H4′′, 2×H5′, 2×H5′′, 2×H6′, 2×H6′′, H3a′, H3a′′, 8×CH_2, cyclopentyl), 2.45–2.62 (m, 2H, 1×H3′, 1×H3′′), 2.65–2.79 (m, 4H, 2×H1, 2×H2), 2.91–3.05 (m, 2H, H6a′, H6a′′), 3.32 (d, *J*=14 Hz, 2H, H2′, H2′′), 3.74 (s, 2H, 2×O*H*); ^{13}C NMR ($CDCl_3$): δ=22.7, 23.8, 24.4, 32.3, 35.2, 35.4, 37.7, 40.7 (C3′, C3′′, C4′, C4′′, C5′, C5′′, C6′, C6′′, 8×*C*H_2, cyclopentyl), 41.2 (C3a′, C3a′′), 53.8 (C1, C2), 72.4, 73.5 (C2′, C2′′, C6a′, C6a′′), 80.1 (2×*C*OH); MS (CI, *i*-butane): *m/z* (%)=417 (100)

[MH^+]; anal. calcd for $C_{26}H_{44}N_2O_2$ (416.3): C, 74.95; H, 10.64; N, 6.72; found: C, 74.32; H, 10.36; N, 6.55.

3.4. (all-R)-1,2-Bis[2-(pentan-3-ol-3-yl)octahydro-cyclopenta[b]pyrrol-1-yl]ethane (all-R)-7

To a freshly prepared Grignard-solution consisting of bromoethane (17.6 g, 161.1 mmol) and magnesium (3.92, 161.1 mmol) in dry THF (300 ml), (*all-R*)-**4** (3.67 g, 10.1 mmol; dissolved in 100 ml of dry THF) is added dropwise at 0–5°C within 0.5 h. The reaction mixture is then heated at reflux temperature for 40 h. The heating bath is removed and a sat. aqueous NH_4Cl-solution (200 ml) is added at room temperature. After phase separation the aqueous layer is extracted with toluene (40 ml). The combined organic phases are dried ($MgSO_4$) and concentrated in vacuo. The crude solid is recrystallized from small amounts of methanol. Yield (not optimized): 1.79 g (42%), colorless solid; mp: 109–111°C; $[\alpha]_D^{20}$=+64.2 (*c* 1.02, CH_2Cl_2); IR (NaCl): ν=3480 cm^{-1} (OH); ^1H NMR ($CDCl_3$, 300 MHz): δ=0.79–0.92 (m, 12H, 4×C*H*$_3$), 1.21–1.36, 1.38–1.76 (2m, 22H, 2×H4′, 2×H4′′, 2×H5′, 2×H5′′, 2×H6′, 2×H6′′, H3a′, H3a′′, 4×C*H*$_2$), 1.82–1.94 (m, 2H, 1×H3′, 1×H3′′), 2.46–2.61 (m, 2H, H3′, H3′′), 2.62–2.76, 2.77–3.00 (2m, 8H, H6a′, H6a′′, 2×H1, 2×H2, 2×O*H*), 3.05–3.17 (m, 2H, H2′, H2′′); ^{13}C NMR ($CDCl_3$): δ=7.7, 8.0 (4×*C*H$_3$), 23.8, 26.2, 30.4, 30.8 (C3′, C3′′, C4′, C4′′, C5′, C5′′, C6′, C6′′), 29.9, 30.8 (4×*C*H$_2$), 40.8 (C3a′, C3a′′), 60.0 (C1, C2), 72.3, 74.1 (C2′, C2′′, C6a′, C6a′′), 74.8 (2×*C*OH); MS (CI, *i*-butane): *m/z* (%)=421 (100) [MH^+]; anal. calcd for $C_{26}H_{48}N_2O_2$ (420.2): C, 74.23; H, 11.50; N, 6.66; found: C, 74.53; H, 10.93; N, 6.60.

3.5. (all-R)-1,2-Bis[2-(1,3-diphenylpropan-2-ol-2-yl)octahydro-cyclopenta[b]pyrrol-1-yl]ethane (all-R)-8

To a suspension of (*all-R*)-2-(octahydro-cyclopenta[*b*]pyrrol-2′-yl)-1,3-diphenylpropan-2-ol[7] (1.5 g, 4.7 mmol) and potassium carbonate (0.64 g, 4.7 mmol) in dry acetonitrile (50 ml), 1,2-dibromoethane (0.44 g, 2.35 mmol) is added dropwise within 30 min at 70°C. Stirring is continued at a constant temperature for 48 h. The solvent is removed in vacuo, the residue dissolved in dichloromethane (60 ml) and washed twice with water (20 ml). After drying with $MgSO_4$ and evaporation of the solvent the resulting crude oil is purified by column chromatography (silica gel 60, eluents: *n*-hexane:ethyl acetate 9:1, with addition of triethylamine (10 ml) per 1 litre of the solvent mixture, TLC: R_f-value: 0.28). The resulting colorless solid is recrystallized from ethanol. Yield (not optimized): 0.56 g (36%); mp: 145–148°C; $[\alpha]_D^{20}$=−38.8 (*c* 1.01, CH_2Cl_2); IR (NaCl): ν=3560 cm^{-1} (OH); ^1H NMR ($CDCl_3$, 300 MHz): δ=1.34–1.74 (m, 16H, H3′, H3′′, 2×H4′, 2×H4′′, 2×H5′, 2×H5′′, 2×H6′, 2×H6′′, H3a′, H3a′′), 2.10–2.24 (m, 4H, 2×H1, 2×H2), 2.39–2.49 (m, 2H, H3′, H3′′), 2.63–2.72, 2.73–2.93 (2m, 8H, 4×C*H*$_2$Ph), 3.10–3.19 (m, 4H, H6a′, H6a′′, 2×O*H*), 3.32 (d, *J*=14 Hz, 2H, H2′, H2′′), 7.16–7.27 (m, 20H, aromat.-H); ^{13}C NMR ($CDCl_3$): δ=24.0, 32.6, 35.2, 35.5 (C3′, C3′′, C4′, C4′′, C5′, C5′′, C6′, C6′′), 40.2, 40.3 (4×*C*H$_2$Ph), 44.8 (C3a′, C3a′′), 54.9 (C1, C2), 70.7, 72.7 (C2′, C2′′, C6a′, C6a′′), 77.2 (2×*C*OH), 126.0, 126.2, 127.8, 128.0, 130.6, 131.1 (2×6 aromat.-C), 137.9, 138.0 (2×2 q. aromat.-C); MS (CI, *i*-butane): *m/z* (%)=669 (100) [MH^+]; anal. calcd for $C_{46}H_{56}N_2O_2$ (668.2): C, 82.59; H, 8.44; N, 4.19; found: C, 83.09; H, 8.42; N, 4.05.

3.6. (all-R)-1,2-Bis[2-(1-phenyl-methanol-yl)octahydro-cyclopenta[b]pyrrol-1-yl]ethane (all-R)-9

To a suspension of (*all-R*)-2-(octahydro-cyclopenta[b]pyrrol-2′-yl)-1′-phenyl-methanol[3d] (0.87 g, 4.0 mmol) and potassium carbonate (0.55 g, 4.0 mmol) in dry acetonitrile (50 ml), 1,2-dibromoethane (0.37

g, 2.0 mmol; in 25 ml dry acetonitrile) is added dropwise within 30 min at 65°C. Stirring is continued at 85°C for 40 h under argon. The solvent is removed in vacuo, the residue dissolved in dichloromethane (50 ml) and washed twice with water (20 ml). After drying with $MgSO_4$ and evaporation of the solvent the resulting crude solid is purified by column chromatography (silica gel 60, eluents: *n*-hexane:triethylamine 9:1, TLC: R_f-value: 0.32). Yield (not optimized): 0.58 g (63%); mp: 94–97°C; $[\alpha]_D^{20}=-4.0$ (*c* 1.00, CH_2Cl_2); IR (NaCl): ν=3040–3280 cm^{-1} (OH); ^1H NMR ($CDCl_3$, 300 MHz): δ=1.32–1.95 (m, 16H, 1×H3′, 1×H3′′, 2×H4′, 2×H4′′, 2×H5′, 2×H5′′, 2×H6′, 2×H6′′, H3a′, H3a′′), 2.32–2.49, 2.52–2.74 (2m, 4H, 2×H1, 2×H2), 2.85–3.19 (m, 6H, 1×H3′, 1×H3′′, 2×C*H*OH, H6a′, H6a′′), 4.61 (d, *J*=14 Hz, 2H, H2′, H2′′), 7.05–7.52 (m, 10H, aromat.-H); ^{13}C NMR ($CDCl_3$): δ=24.3, 32.3, 34.0, 37.5 (C3′, C3′′, C4′, C4′′, C5′, C5′′, C6′, C6′′), 40.5 (C3a′, C3a′′), 57.1 (C1, C2), 73.0, 75.6 (C2′, C2′′, C6a′, C6a′′), 76.2 (2×*C*OH), 126.2, 126.9, 128.1 (2×3 aromat.-C), 143.9 (2×1 q. aromat.-C); MS (CI, *i*-butane): *m/z* (%)=461 (100) [MH^+]; anal. calcd for $C_{30}H_{40}N_2O_2$ (460.2): C, 78.22; H, 8.75; N, 6.08; found: C, 78.04; H, 8.66; N, 5.98.

*3.7. (*all-S*)-1,2-Bis[2-(cyclopentan-1-ol-1-yl)pyrrolidon-1-yl]ethane (*all-S*)-**10***

To a suspension of (*S*)-1′-(pyrrolidin-2-yl)cyclopentanol[9] (2.0 g, 12.9 mmol) and potassium carbonate (1.78 g, 12.9 mmol) in dry acetonitrile (150 ml), 1,2-dibromoethane (1.2 g, 6.45 mmol; in 25 ml dry acetonitrile) is added dropwise within 30 min at 80°C. Stirring is continued at 80°C for 48 h under argon atmosphere. The solvent is removed in vacuo, the residue dissolved in dichloromethane (50 ml) and washed twice with water (20 ml). After drying and evaporation of the solvent the resulting crude oil is purified by column chromatography (silica gel 60, eluent: *n*-hexane:ethyl acetate:triethylamine 8:1:1, TLC: R_f-value: 0.42). Yield (not optimized): 0.46 g (21%), highly viscous oil; $[\alpha]_D^{20}=-27.2$ (*c* 2.05, CH_2Cl_2); IR (NaCl): ν=3300–3500 cm^{-1} (OH); ^1H NMR ($CDCl_3$, 300 MHz): δ=1.35–1.85 (m, 24H, 8×C*H*$_2$, 2×H3′, 2×H3′′, 2×H4′, 2×H4′′), 2.32–2.41, 2.45–2.63 (2m, 4H, 2×H1, 2×H2), 2.70–2.82, 2.85–3.05 (2m, 4H, 2×H5′, 2×H5′′), 3.12–3.15 (m, 2H, H2′, H2′′), 3.92 (s, 2H, 2×O*H*); ^{13}C NMR ($CDCl_3$): δ=23.6, 24.0, 25.2, 28.0 (8×C, cyclopentyl), 35.6, 38.6 (C3′, C3′′, C4′, C4′′), 56.0, 58.6 (C1, C2, C5′, C5′′), 71.9 (C2′, C2′′), 84.2 (2×*C*OH); MS (CI, *i*-butane): *m/z* (%)=337 (100) [MH^+]; anal. calcd for $C_{20}H_{36}N_2O_2$ (336.4): C, 71.38; H, 10.78; N, 8.32; found: C, 71.24; H, 10.43; N, 8.15.

3.8. General procedure

Enantiocontrolled addition of diethylzinc to benzaldehyde in the presence of catalytic amounts of amino alcohols **5**–**14** (the results are summarized in Table 1) is described below.

Under argon atmosphere a solution of 1.0 mmol of the respective catalyst precursor (alternatively 0.5, 0.25 or 0.1 mmol, i.e. 10, 5, 2 or 1 mol% of amino alcohols **5**–**14**) in anhydrous toluene (20 ml) 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 min. After 30 min with stirring at constant temperature the clear solution is allowed to warm to room temperature. Then freshly distilled benzaldehyde (1.06 g, 10 mmol), dissolved in anhydrous toluene (20 ml), is added over a 30-min period. The mixture is stirred for an additional 40 h and quenched at 0°C by the addition of 60 ml 2N 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 of 1-phenylpropan-1-ol: between 29 and 82%). The enantiomeric excess (*ee*) is determined by chiral GC analysis performed on a Shimadzu GC-

15a instrument (25 m chiral column: SGE Cydex-B, ω_i=0.25 mm, film thickness: 0.25 μm, 1 μl product in *n*-hexane, detection: FID, carrier gas: nitrogen).

Acknowledgements

We express our thanks to Degussa AG, Hoechst AG, Witco GmbH and the Fonds der Chemischen Industrie for generously providing the chemicals and for financial support.

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