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New C_2-symmetric 2,4-bis(1-hydroxycyclopentyl)azetidines derived from (*S*)-1-phenylethylamine and their application in the enantioselective catalysis

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Abstract

The synthesis of new tridental 2,4-bis(1-hydroxycyclopentyl)azetidines using (*S*)-1-phenylethylamine as starting material is described. These new structures have been successfully applied in the enantiocontrolled catalytic addition of diethylzinc to aromatic aldehydes reaching enantiomeric excesses of up to 85% for the resulting 1-arylpropan-1-ols. Attempts in the field of the enantioselective oxazaborolidine-catalyzed reduction of ketones employing azetidine alcohols as precatalysts are also included.

1. Introduction

Even though particularly efficient ligands for the enantiocontrolled ethylation by diethylzinc have been reported, the design of new ligands has been continuously attracting research interest.[1] In fact, from a practical viewpoint, it is still of strong current interest to develop highly effective ligands meeting levels suitable for practical application.

Prompted by recent reports on the application of tridental, small-ring heterocycles such as aziridine alcohols[2] and 2,5-disubstituted pyrrolidine derivatives,[3] we considered the utilization of C_2-symmetric azetidinyl-methanols[4] as chiral catalysts in the addition of diethylzinc to aldehydes. Here we report a facile synthesis of stereoisomeric pairs of 2,4-bis(1-hydroxycyclopentyl)azetidins bearing two cyclopentanol substituents on the carbon atoms adjacent to the nitrogen. In addition, results of their application as catalysts in two asymmetric transformations are described.

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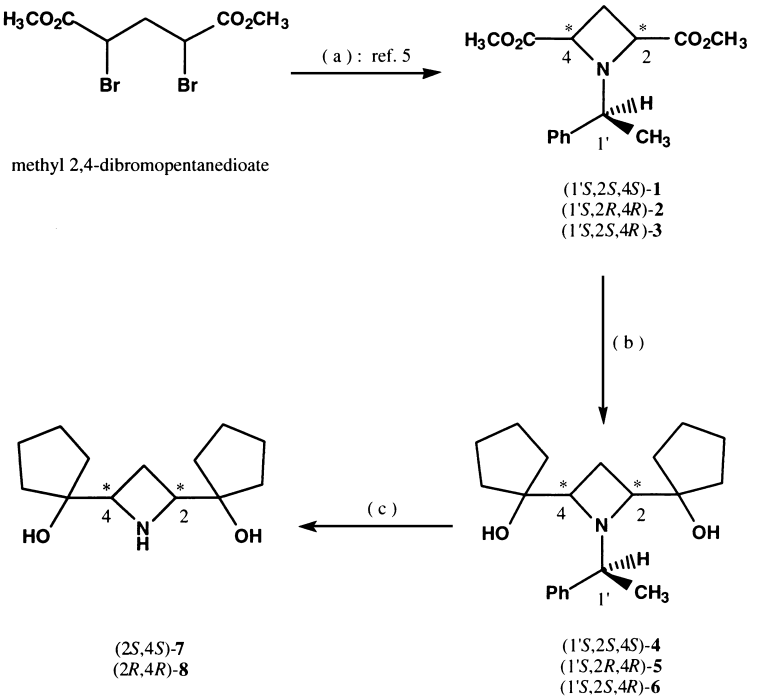
2. Results and discussion

The synthesis of aminoalcohols **4–6** and **7**, **8** is accomplished in a two- or three-step sequence starting from (*S*)-1-phenylethylamine (see Scheme 1 depicted below). Diastereomers **1–3** of known configuration are available by Yamamoto's procedure[5] via ring-closure reaction with methyl 2,4-dibromopentanedioate (Scheme 1). Each diastereomer is converted to the corresponding bis(cyclopentanol) structure **4–6** by reaction of the respective diester with an excess of 5 equiv. of the difunctional Grignard reagent 1,4-bis(bromomagnesio)butane in THF with yields ranging from 54 to 82%.[6] Finally, catalytic hydrogenolysis of (1′*S*,2*S*,4*S*)-**4** and (1′*S*,2*R*,4*R*)-**5** over palladium hydroxide on carbon gives the secondary amines (2*S*,4*S*)-**7** (yield: 49%) and (2*R*,4*R*)-**8** (45%), respectively.



Scheme 1. (a) See Ref. 5; (b) 5 equiv. of $BrMg(CH_2)_4MgBr$ in THF at reflux temperature for 18 h, purification by column chromatography (silica gel, eluents: *n*-hexane/ethyl acetate), isolated yields: (1′*S*,2*S*,4*S*)-**4**: 82%, (1′*S*,2*R*,4*R*)-**5**: 68% and (1′*S*,2*S*,4*R*)-**6**: 54%; (c) (1) $H_2/Pd(OH)_2/C$ 24 h at room temperature in MeOH, (2) purification by column chromatography (silica gel, eluents: ethyl acetate:ethanol 3:7), isolated yields: (2*S*,4*S*)-**7**: 49% and (2*R*,4*R*)-**8**: 45%

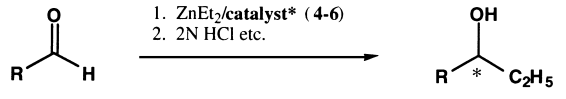
The enantioselective addition of diethylzinc to various aromatic aldehydes has been conducted in the presence of the optically active (pre-)catalysts **4–6** (Table 1 gives a summary of the results). In a typical procedure the reaction was carried out at –30 to 110°C for 40 h with a catalyst concentration of 2–20 mol% relative to the respective aldehyde. In general, the chemical yields obtained after fractional distillation ranged from moderate to good (61–85%, with the exception of entries 14 and 15). The process optimization with respect to the reaction temperature and the catalyst concentration using benzaldehyde as a model substrate is described in entries 1–9. Entry

2 displays the best result in terms of enantioselectivity. At a reaction temperature of 0°C with 10 mol% of ligand **4** the ethylation product **10a** is obtained in 76% chemical yield and 77% *e.e.*[7] The differences in comparison with entries 8 and 9 — employing a catalyst concentration of 5 and 20 mol% — are only marginal (73 and 75% *e.e.*, respectively).

Table 1
Enantioselective addition of diethylzinc to aromatic aldehydes (substrates **9a–e**, see Scheme 2 depicted above) catalyzed by ligands **4–6**; products: 1-phenylpropan-1-ol **10a**, 1-(4-chlorophenyl)propan-1-ol **10b**, 1-(4-methylphenyl)propan-1-ol **10c**, 1-(4-methoxy-phenyl)propan-1-ol **10d** and 1-(2-furanyl)propan-1-ol **10e**

Entry	Substrate [**9a-e**]	Catalyst*	Cat. conc. [mol%]	Temp. [°C]	Yield[b] [%]	$[\alpha]_{20;}^{D}$ (*c*)	*o.p./e.e.*[7] [%]	Config[c-g]
1	**9a**	**4**	10	-30	61	-34.1 (5.12)[c]	75	(*S*)
2	**9a**	**4**	10	0[a]	76	-35.2 (5.25)[c]	77	(*S*)
3	**9a**	**4**	10	25	82	-29.6 (5.07)[c]	65	(*S*)
4	**9a**	**4**	10	50	73	-27.9 (5.23)[c]	61	(*S*)
5	**9a**	**4**	10	80	76	-22.9 (5.15)[c]	50	(*S*)
6	**9a**	**4**	10	110	71	-19.6 (5.08)[c]	43	(*S*)
7	**9a**	**4**	2	0[a]	62	-15.1 (5.15)[c]	33	(*S*)
8	**9a**	**4**	5	0[a]	74	-33.1 (5.13)[c]	73	(*S*)
9	**9a**	**4**	20	0[a]	85	-33.9 (5.20)[c]	75	(*S*)
10	**9a**	**5**	10	0[a]	79	+33.2 (5.24)[c]	73	(*R*)
11	**9a**	**6**	10	0[a]	68	+4.1 (5.04)[c]	9	(*R*)
12	**9b**	**4**	5	0[a]	64	-8.9 (4.93)[d]	85	(*S*)
13	**9c**	**4**	5	0[a]	77	-26.2 (5.06)[e]	67	(*S*)
14	**9d**	**4**	5	0[a]	24	-7.9 (4.88)[f]	46	(*S*)
15	**9e**	**4**	5	0[a]	37	-1.0 (2.03)[g]	8	(*S*)

[a]: 6 h at 0 °C, then the reaction mixture was allowed to slowly warm to room temp.; [b]: Isolated yield after fractional distillation; [c]: measured in chloroform, specific rotation referred to $[\alpha]_{20;}^{D}$ = 45.45 (*c*=5.15, $CHCl_3$) for (*S*)-1-phenylpropan-1-ol **10a**[8]; [d]: measured in benzene, specific rotation referred to $[\alpha]_{20;}^{D}$ = -10.4 (*c*=5.0, benzene) for (*S*)-1-(4-chlorophenyl)propan-1-ol **10b** in 43% *e.e.*[9]; [e]: measured in benzene, specific rotation referred to $[\alpha]_{20;}^{D}$ = -39.2 (c=5.10, benzene) for (*S*)-1-(4-methylphenyl)propan-1-ol **10c**[10]; [f]: measured in benzene, specific rotation referred to $[\alpha]_{20;}^{D}$ = -17.2 (*c*=5.0, benzene) for (*S*)-1-(4-methoxyphenyl)-propan-1-ol **10d** in 51% *e.e.*[11]; [g]: measured in chloroform, specific rotation referred to $[\alpha]_{20;}^{D}$ = +12.6 (*c*=2.09, $CHCl_3$) for (*R*)-1-(2-furanyl)propan-1-ol **10e** in 95% *e.e.*[12].



9a (R = Phenyl)
9b (R = 4-Chloro-phenyl)
9c (R = 4-Methyl-phenyl)
9d (R = 4-Methoxy-phenyl)
9e (R = 2-Furanyl)

10a (R = Phenyl)
10b (R = 4-Chloro-phenyl)
10c (R = 4-Methyl-phenyl)
10d (R = 4-Methoxy-phenyl)
10e (R = 2-Furanyl)

Scheme 2. Enantioselective catalytic ethylation of various aldehydes in the presence of the optically active catalysts **4–6**

Furthermore, ligand **4** was also successfully tested for the conversion of other aromatic aldehydes **9b–e** with a maximum *e.e.* value of 85% for the formation of 1-(4-chlorophenyl)propan-1-ol **10b** (entry 12).

A comparison between the structures **4**, **5** and **6** (entries 2, 10 and 11) reveals the minor influence of the third, (*S*)-1-phenylethylamine derived stereogenic center on the asymmetric induction. The best result is obtained with an (*all-S*)-configuration of the three internal stereogenic centers in ligand **4** (entry 2) with a predominant formation of the (*S*)-configurated ethylation product in 77% *e.e.* By changing to a less favored situation in terms of inductive capability (ligand **5**) an only slightly diminished result (entry 10: 73% *e.e.*) together with a (*R*)-configuration of the addition product is obtained. As expected structure **6** gives only a very low *e.e.* value (entry 11: 9% *e.e.*).

A second application chosen to test the inductive capabilities of the new structures is the homogeneous catalytic reduction of various aromatic ketones with in situ formed oxazaborolidine catalysts[8] derived from enantiomerically pure ligands **7** and **8**, respectively. The conversion of these β-amino bis-alcohols to oxazaborolidines is accomplished by treatment with BH_3/THF. No further purification or characterization of the resulting intermediate was carried out. In a representative procedure 1–5 mol% of **7** or **8** in THF are employed as precatalysts at a reaction temperature of +30°C in the reduction of acetophenone, ω-chloro-acetophenone or propiophenone. In general, good chemical yields (76 to 91% after distillation) are reached whereas the corresponding enantioselectivities are moderate to low with *e.e.* values only ranging from 35 to 54%.

In conclusion, the synthesis of a family of simple, tricyclic azetidine alcohols is described which are attractive because of their ready availability in both enantiomeric forms (**7** and **8**) and due to their beneficial structural features (C_2-symmetry, limited flexibility). These new chiral structures efficiently catalyze the diethylzinc addition to aromatic aldehydes with up to 85% *e.e.*, which is slightly below the results reported by Shi et al.[4] for related C_2-symmetric azetidines bearing two flexible methoxy groups.

3. Experimental

All reactions were carried out in oven dried glassware under an 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 ^1H 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 enantiocontrolled diethylzinc reactions[9] and the oxazaborolidine catalyzed reductions[10] were conducted according to previously published procedures.

*3.1. General procedure: conversion of **1–3** to **4–6** with 1,4-bis(bromomagnesio)butane*

To a freshly prepared Grignard reagent generated from 1.54 g (63.1 mmol) magnesium and 6.81 g (31.6 mmol) 1,4-dibromobutane in 50 ml dry THF is added dropwise a solution of

1.75 g (6.3 mmol) of compounds **1**–**3**[5] in 10 ml THF at room temperature. After the addition, the reaction mixture is stirred at reflux temperature for 18 h. Then the reaction is hydrolyzed with an aqueous solution of NH_4Cl and the aqueous phase is extracted twice with 30 ml of diethyl ether. The combined organic layers are washed with brine, dried with magnesium sulfate and concentrated in vacuo. The resulting crude products are purified by column chromatography on silica gel.

*3.1.1. (1′*S*,2*S*,4*S*)-1-[(*S*)-1′-Phenethyl]-2,4-bis(1-hydroxycyclopentyl)azetidine (1′*S*,2*S*,4*S*)-**4**

Column chromatography: *n*-hexane:ethyl acetate 6:4 (R_f-value: 0.54). Yield: 1.70 g (82%), colorless solid; mp: 126–128°C; $[\alpha]_D^{20} = -52.0$ ($c = 1.01$, $CHCl_3$); IR (KBr): $\nu = 3640$–3410 cm^{-1} (OH); ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.11$–1.88 (m, 16H, 8×CH_2, cyclopentyl), 1.28 (d, $J = 7.1$ Hz, 3H, PhCHCH_3), 2.00–2.20 (m, 2H, CH_2), 2.85 (s, 2H, O*H*), 3.65–3.80 (m, 2H, 2×C*H*), 4.45 (q, $J = 7.1$ Hz, 1H, PhC*H*CH_3), 7.10–7.40 (m, 5H, aromat.-H); ^{13}C NMR ($CDCl_3$): $\delta = 23.04$ (PhCH*C*H_3), 23.52, 25.20, 37.51, 40.55 (9×*C*H_2), 56.23 (Ph*C*HCH$_3$), 66.92 (2×*C*H), 82.97 (2×*C*OH), 126.17, 126.42, 128.41 (aromat.-C), 146.55 (q. aromat.-C); MS (CI, *i*-butane): m/z (%) = 330 (100) [MH^+]. Anal. calcd for $C_{21}H_{31}NO_2$ (329.5): C, 76.55; H, 9.48; N, 4.25; found: C, 76.40; H, 9.48; N, 3.98.

*3.1.2. (1′*S*,2*R*,4*R*)-1-[(*S*)-1′-Phenethyl]-2,4-bis(1-hydroxycyclopentyl)azetidine (1′*S*,2*R*,4*R*)-**5**

Column chromatography: *n*-hexane:ethyl acetate 2:8 (R_f-value: 0.45). Yield: 1.41 g (68%), slightly colored solid; mp: 113°C; $[\alpha]_D^{20} = +5.1$ ($c = 1.04$, $CHCl_3$); IR (KBr): $\nu = 3635$–3400 cm^{-1} (OH); ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.11$–1.92 (m, 16H, 8×CH_2, cyclopentyl), 1.45 (d, $J = 7.1$ Hz, 3H, PhCHCH_3), 1.96–2.07 (m, 2H, CH_2), 2.77 (s, 2H, O*H*), 3.69–3.80 (m, 2H, 2×C*H*), 4.44 (q, $J = 7.1$ Hz, 1H, PhC*H*CH_3), 7.20–7.47 (m, 5H, aromat.-H); ^{13}C NMR ($CDCl_3$): $\delta = 19.25$ (PhCH*C*H_3), 23.06, 23.28, 25.03, 37.26, 39.10 (9×*C*H_2), 55.23 (Ph*C*HCH$_3$), 66.78 (2×*C*H), 82.67 (2×*C*OH), 127.39, 128.21, 128.85 (aromat.-C), 141.47 (q. aromat.-C); MS (CI, *i*-butane): m/z (%) = 330 (100) [MH^+]. Anal. calcd for $C_{21}H_{31}NO_2$ (329.5): C, 76.55; H, 9.48; N, 4.25; found: C, 76.32; H, 9.55; N, 4.13.

*3.1.3. (1′*S*,2*S*,4*R*)-1-[(*S*)-1′-Phenethyl]-2,4-bis(1-hydroxycyclopentyl)azetidine (1′*S*,2*S*,4*R*)-**6**

Column chromatography: *n*-hexane:ethyl acetate 1:1 (R_f-value: 0.54). Yield: 1.12 g (54%), viscous oil; $[\alpha]_D^{20} = +7.3$ ($c = 8.35$, $CHCl_3$); IR (KBr): $\nu = 3620$–3400 cm^{-1} (OH); ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 1.17$–1.95 (m, 18H, 8×CH_2, cyclopentyl, CH_2, azetidine ring), 1.50 (d, $J = 7.1$ Hz, 3H, PhCHCH_3), 2.80 (s, 2H, O*H*), 3.24–3.41 (m, 2H, 2×C*H*), 3.85 (q, $J = 7.1$ Hz, 1H, PhC*H*CH_3), 7.18–7.40 (m, 5H, aromat.-H); ^{13}C NMR ($CDCl_3$): $\delta = 16.54$ (PhCH*C*H_3), 20.67, 23.16, 24.43, 24.49, 35.37, 35.48, 38.82, 39.01 (9×*C*H_2), 60.00, 62.76, 65.21 (3×*C*H), 82.06, 82.26 (2×*C*OH), 127.35, 127.97, 128.37 (aromat.-C), 142.81 (q. aromat.-C); MS (CI, *i*-butane): m/z (%) = 330 (100) [MH^+]. Anal. calcd for $C_{21}H_{31}NO_2$ (329.5): C, 76.55; H, 9.48; N, 4.25; found: C, 76.25; H, 9.40; N, 4.01.

*3.2. General procedure: synthesis of β-aminodiols **7** and **8** by catalytic hydrogenolysis of **4** and **5***

A suspension of 1.47 g (4.46 mmol) of (1′*S*,2*S*,4*S*)-**4** or (1′*S*,2*R*,4*R*)-**5** dissolved in 30 ml methanol and palladium hydroxide on charcoal is stirred under hydrogen atmosphere for 24 h at room temperature. The catalyst is filtered off and washed twice with 50 ml methanol. The combined methanol solutions are concentrated under reduced pressure yielding green, viscous oils. These

crude products are further purified by column chromatography (silica gel 60) utilizing ethyl acetate and ethanol in a ratio of 3:7 as eluents.

3.2.1. (2S,4S)-2,4-Bis(1-hydroxycyclopentyl)azetidine (2S,4S)-7

Yield: 0.49 g (49%), colorless solid; mp: 127°C; $[\alpha]_D^{20} = -40.2$ ($c = 1.00$, $CHCl_3$); IR (KBr): $\nu = 3620–3110$ cm^{-1} (OH, NH); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.30–2.00$ (m, 16H, 8×CH_2, cyclopentyl), 2.20–2.29 (m, 2H, CH_2), 3.20 (s, 2H, 2×O*H*), 3.60–3.70 (m, 2H, 2×C*H*); ^{13}C NMR ($CDCl_3$): $\delta = 22.89$, 24.25, 24.47, 35.32, 37.67 (9×*C*H$_2$), 62.35 (2×*C*H), 82.55 (2×*C*OH); MS (CI, *i*-butane): m/z (%) = 226 (100) [MH$^+$]. Anal. calcd for $C_{13}H_{23}NO_2$ (225.3): C, 69.30; H, 10.29; N, 6.22; found: C, 69.55; H, 10.41; N, 5.92.

*3.2.2. (2R,4R)-2,4-Bis(1-hydroxycyclopentyl)azetidine (2R,4R)-**8***

Yield: 0.38 g (45%), colorless solid; mp: 125°C; $[\alpha]_D^{20} = +37.8$ ($c = 1.05$, $CHCl_3$); IR (KBr): $\nu = 3640–3120$ cm^{-1} (OH, NH); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.30–1.91$ (m, 16H, 8×CH_2, cyclopentyl), 2.30–2.40 (m, 2H, CH_2), 3.73–3.83 (m, 2H, 2×C*H*), 4.67 (s, 2H, 2×O*H*); ^{13}C NMR ($CDCl_3$): $\delta = 22.29$, 24.23, 24.56, 35.32, 37.76 (9×*C*H$_2$), 63.15 (2×*C*H), 81.60 (2×*C*OH); MS (CI, *i*-butane): m/z (%) = 226 (100) [MH$^+$]. Anal. calcd for $C_{13}H_{23}NO_2$ (225.3): C, 69.30; H, 10.29; N, 6.22; found: C, 69.04; H, 10.11; N, 6.43.

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