Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1313–1321

TETRAHEDRON: *ASYMMETRY*

Chiral aminoalcohols with a menthane skeleton as catalysts for the enantioselective addition of diethylzinc to benzaldehyde†

Stefan Panev,[a] Anthony Linden[b] and Vladimir Dimitrov[a,*]

[a]*Institute of Organic Chemistry, Bulgarian Academy of Sciences, BG-1113 Sofia, Bulgaria*
[b]*Institute of Organic Chemistry, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland*

Received 17 April 2001; accepted 8 May 2001

Abstract—Novel chiral aminoalcohols were synthesized by highly diastereoselective addition of Me_3SiCN and $LiCH_2CN$ to (−)-menthone followed by $LiAlH_4$ reduction. The addition of CH_2=CH-MgBr and PhCH=CH-MgBr to menthone and the following epoxidation, provided useful hydroxy epoxides, one of which could be aminolyzed to afford an aminodiol. In one case, the configuration of the newly formed epoxidic stereogenic center was determined by X-ray crystallography. When applied as catalysts in the enantioselective addition of Et_2Zn to benzaldehyde, the aminoalcohols induced enantiomeric excesses (e.e.s) of up to 77%.

1. Introduction

Catalytic asymmetric carbon–carbon bond formation has been one of the most studied fields in synthetic organic chemistry over recent years.[1–3] The enantioselective addition of dialkylzinc compounds to aldehydes in reactions catalyzed by different types of chiral ligands has been investigated intensively because the preparation of enantiomerically pure or enriched alcohols is of considerable interest for the synthesis of bioactive compounds and natural products.[4] Aminoalcohols have been shown to be highly efficient chiral catalysts and among them the β-aminoalcohols have been thought to provide the best results. In general, since Noyori demonstrated the high activity of (−)-3-*exo*-dimethylaminoisoborneol and suggested a mechanistic model for the catalytic cycle, β-aminoalcohols have usually been employed.[5] Until recently, only a few examples of the use of γ-[6] and δ-aminoalcohols[7,8] have been reported. However, there has been increased interest in the preparation of δ-aminoalcohols, and their utility as catalysts for the asymmetric addition of dialkylzincs to aldehydes has been demonstrated.[9] The δ-aminoalcohol *N*,*N*-dimethylaminopropyl neomenthol,[8] prepared in one step by the addition of dimethylaminopropyl lithium to (−)-menthone, catalyzed the enantioselective addition of diethylzinc to several aldehydes with excellent enantioselectivities of up to 95%. We were therefore interested in preparing (−)-menthone derived β- and γ-aminoalcohols and testing them as chiral ligands.

The synthetic strategy used for the study presented herein was developed during recent investigations.[10] This strategy involves the addition of suitable organometallic reagents to (−)-menthone, which proceeds highly diastereoselectively,[11] and further transformation of the products to afford the desired aminoalcohols.

2. Results and discussion

The first step in the investigation was, based on previous experiences,[10] the addition of Me_3SiCN, $LiCH_2CN$, CH_2=CH-MgBr and PhCH=CH-MgBr to (−)-menthone. For a successful reaction with Me_3SiCN, the (−)-menthone **1** needed to be activated with an equimolar quantity of $BF_3{\cdot}OEt_2$. Interestingly, the attack of the reagent occurred predominantly from the axial face of the menthane skeleton leading to the axial and equatorial addition products presented in Scheme 1. In the case of the equatorial addition product, it was not possible during the hydrolytic work-up to cleave completely the initially formed silyl ether **3**, to give the corresponding cyanohydrin **2** (ratio **2**:**3**:**4** = 20:11:69 in

* Corresponding author. E-mail: vdim@orgchm.bas.bg
† Dedicated to Professor Heinz Heimgartner on the occasion of his 60th birthday.

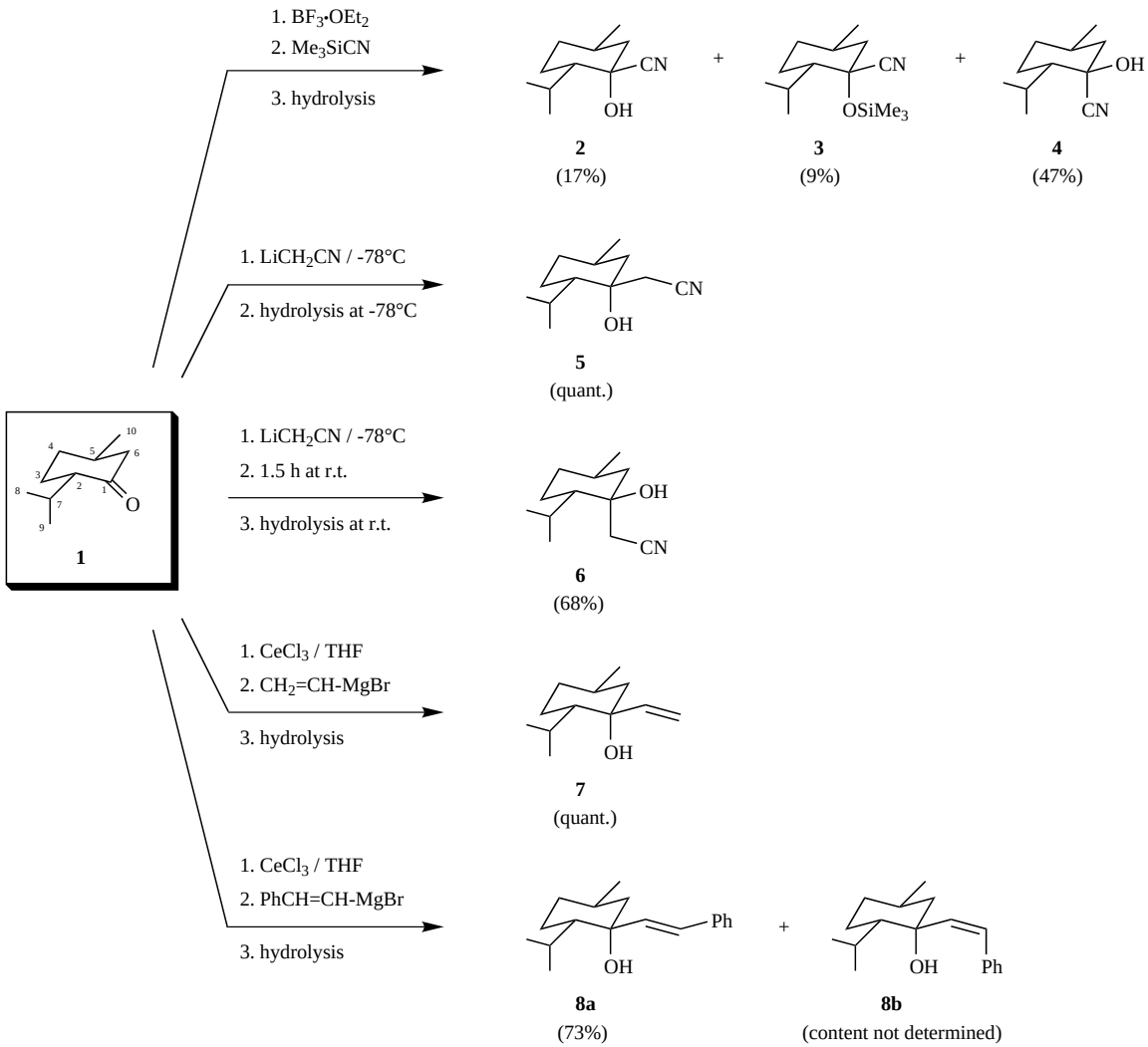
0957-4166/01/$ - see front matter
PII: S0957-4166(01)00206-3

the crude product by NMR). Similar behavior was observed in the addition of the $Me_3SiCN/BF_3{\cdot}OEt_2$ reagent to (+)-camphor and (−)-fenchone.[10g] The compounds **2**, **3** and **4** could be isolated after column chromatography in the yields given in Scheme 1.

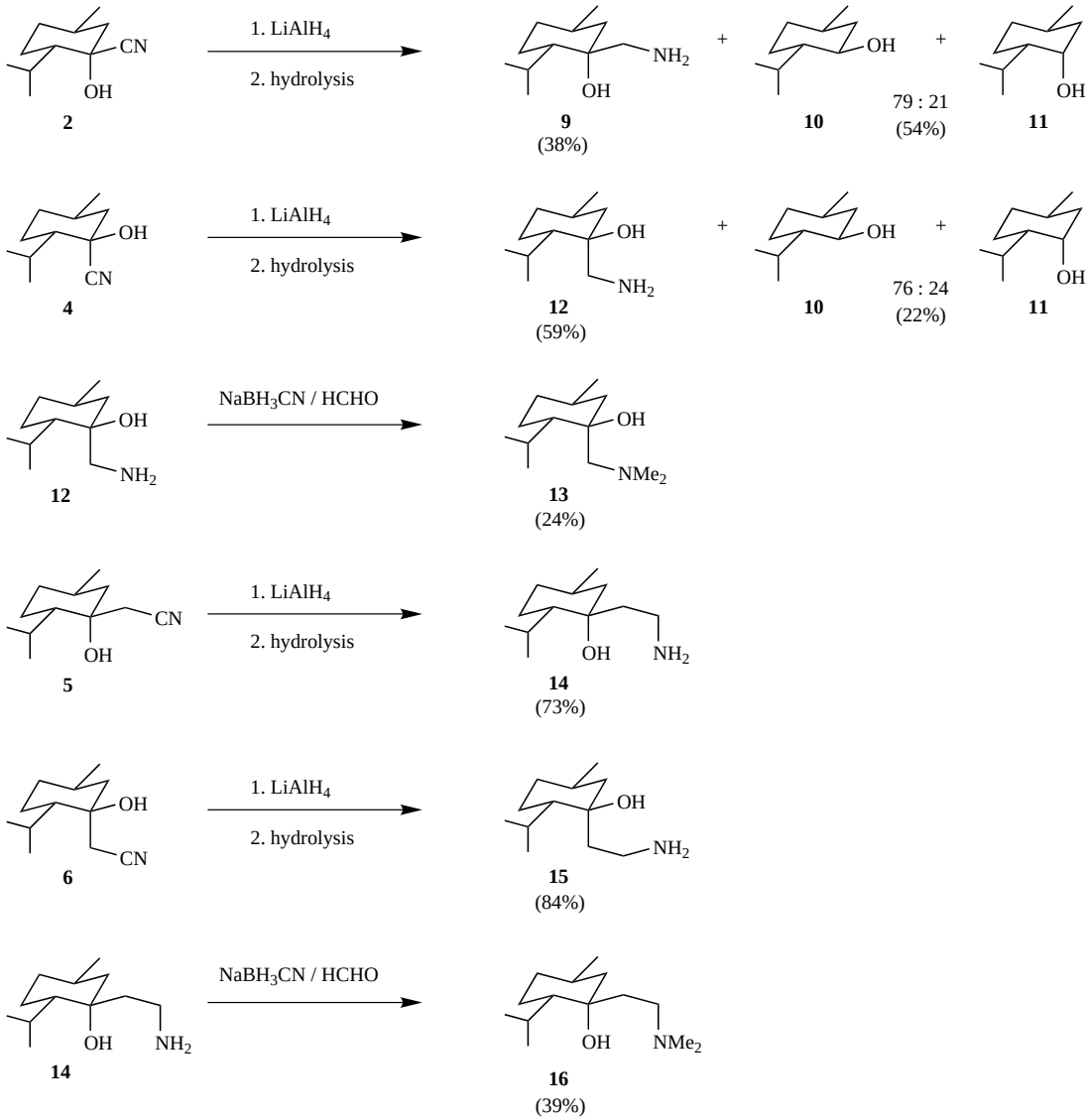
As described previously,[11a] the addition of $LiCH_2CN$ to **1** afforded compounds **5** and **6** in excellent yields, depending on the reaction conditions. Compound **5** could be isolated with 92% d.e.; however, **6** was obtained in a diastereoisomerically pure form after simple recrystallization.[11a] In an earlier work,[12] CH_2=CH-MgBr was added to **1** to give 92% of **7**, 4% of its diastereoisomer formed as a result of axial attack of the reagent, and 4% of unreacted menthone was returned. However, it was reported later[13] that the same reaction proceeds exclusively from the equatorial side of the carbonyl group, with only 77% yield. In the present investigation, compound **7** was prepared by the addition of the vinyl Grignard reagent to (−)-menthone, activated with anhydrous $CeCl_3$, which was prepared and applied according to our recently published procedure.[10a,10d,11b] In this manner, compound **7** was obtained quantitatively as a single diastereoisomer (as determined by NMR).

The addition of PhCH=CH-MgBr, prepared from magnesium and β-bromostyrene (mixture of *trans*/*cis*-isomers = 85:15), to $CeCl_3$ activated **1** provided a mixture of the equatorial addition products **8a** and **8b**, from which **8a** was isolated in 73% yield after column chromatography. Compound **8a** has been reported previously;[14] however, no experimental or analytical data is available.

For the preparation of β-aminoalcohols (Scheme 2) compounds **2** and **4** were reduced with $LiAlH_4$ to the corresponding **9** and **12**, which were isolated in moderate yields (38 and 59%, respectively). Unfortunately, in both cases, considerable amounts of menthol **10** and neomenthol **11** were also isolated. This indicates the formation of menthone as a side product under the reaction conditions, which gives **10** and **11** on reduction. The cyanomethyl addition products **5** and **6** were reduced to the corresponding γ-aminoalcohols **14** and **15**, respectively, with very good yields. The preparation of *N*,*N*-dimethylaminoalcohols succeeded only in the case of **13** and **16**, however in low yields, by the reaction of $NaBH_3CN$/HCHO with **12** and **14**, respectively.



Scheme 1.



Scheme 2.

The allylic alcohols **7** and **8a** were epoxidized with *tert*-butyl hydroperoxide and $VO(acac)_2$ as catalyst to the corresponding hydroxy epoxides **17** and **18** in very good yields and diastereoselectivity (98% d.e. for **17** and 82% d.e. for **18** in the crude product). The pure diastereoisomers were obtained after column chromatography.

The configuration of the newly formed stereogenic centers in **18** was determined by X-ray crystallographic analysis (Fig. 1), where the known (*S*)-configuration at C(2) was used to define the enantiomer employed in the model for the crystal structure refinement. Therefore, the hydroxy group directed V^{5+}-promoted epoxidation occurs, in accordance with the cyclic transition state,[16] from the *re*-side of the double bond (Scheme 3). The *si*-face is obviously highly hindered by the *iso*-propyl group of the menthane skeleton. Therefore, we assume that the predominantly formed diastereoisomer **17** also has (*R*)-configuration at the epoxide stereogenic center. So far we have been unable to obtain crystals of **17** of sufficient quality for X-ray crystal structure analysis.

The aminolysis of **17** with Et_2NH in the presence of $LiClO_4$ afforded aminodiol **19** in only 19% yield. The cleavage proceeded with excellent regioselectivity at the less substituted carbon atom of the epoxide and therefore, with retention of the configuration, according to previously published data.[10f,17] Attempts to aminolyze the hydroxy epoxide **18** with Et_2NH in the presence of metal salts or with $LiAl(NEt_2)_4$ in THF were unsuccessful.

The aminoalcohols **9**, **12**–**16** and **19** were applied as catalysts (3 mol%) in the enantioselective addition of diethylzinc to benzaldehyde (Table 1). The addition reactions were carried out in hexane with 1 M solution of Et_2Zn in hexane according to the published procedure.[10f] The yields of the isolated 1-phenyl-1-propanol

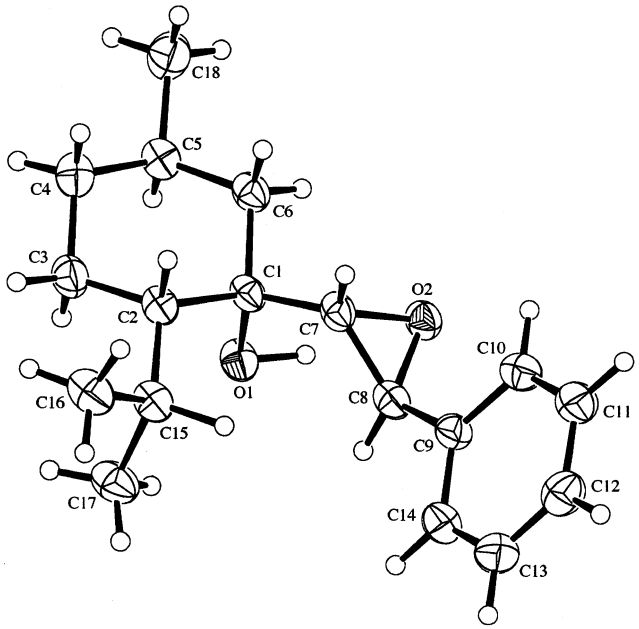


Figure 1. ORTEP[15] plot of the molecular structure of **18** with 50% probability ellipsoids.

were high. The observed enantioselectivities were low to moderate and in all cases the (*S*)-enantiomer was formed predominantly. The best result was realized with the γ-aminoalcohol **16**. It is important to note that the enantioselectivity obtained with *N*,*N*-dimethyl-aminoalcohol **13** was lower than with the corresponding aminoalcohol **12**, while **16** which is the *N*,*N*-dimethyl analogue of **14** increased the asymmetric induction remarkably.

The unambiguous assignment of the proton and carbon-13 spectra (Table 2 and Section 3) was made on the basis of DEPT, HSQC[18] and NOESY experiments.

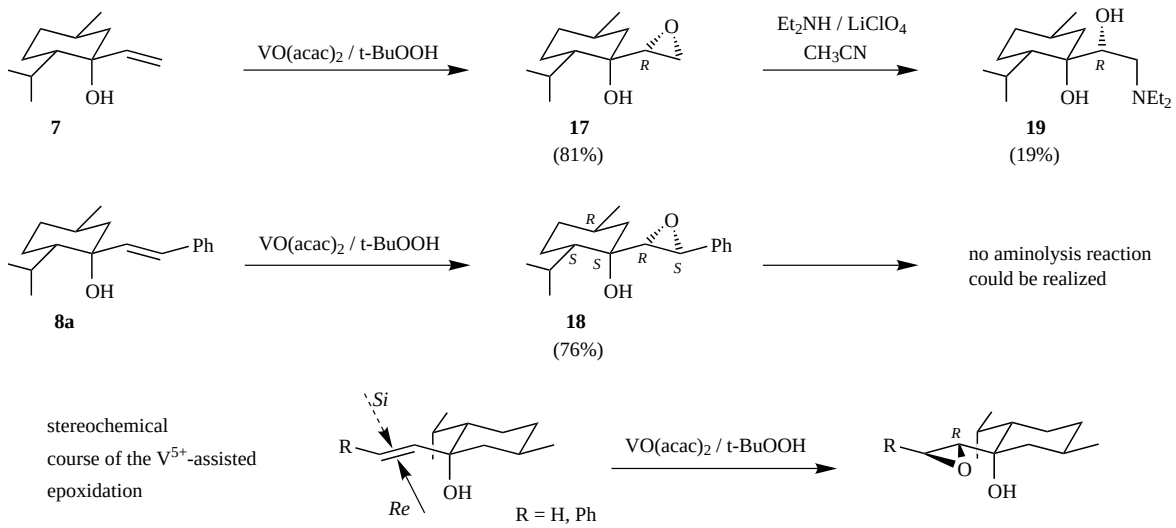
In conclusion, we have prepared some new enantiomerically pure derivatives (cyanohydrins, hydroxy epoxides, aminoalcohols) starting from (–)-menthone and by using relatively simple transformation reactions. The aminoalcohols provided only moderate enantioselectivity for the addition of Et_2Zn to benzaldehyde. The preparation of further derivatives with possibly better efficiency as chiral catalysts is in progress.

3. Experimental

3.1. General methods and starting materials

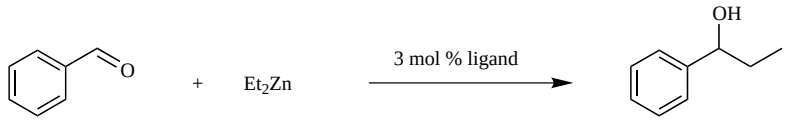
The reactions with air and moisture sensitive reagents were carried out in flame-dried Schlenk flasks under an argon atmosphere. The solvents were dried (sodium/benzophenone for Et_2O and THF) and distilled. Thin-layer chromatography (TLC) was performed using aluminum sheets precoated with silica gel 60 F_{254} (Merck). Column chromatography was carried out at normal pressure, silica gel 60 (0.063–0.200 mm, Merck). Melting points were obtained using a Kofler block apparatus (uncorrected). $[\alpha]_D^{20}$ measurements were obtained using a Perkin–Elmer 241 polarimeter. Mass spectra (MS) analyses were obtained using a Finnigan MAT 90 or Finnigan SSQ 700 and are reported as fragmentation in *m*/*z* with relative intensities (%) in parentheses. NMR spectra were recorded on a Bruker Avance DRX-250 (^1H at 250.1 MHz; ^{13}C at 62.9 MHz; TMS as internal standard); samples for NOE difference experiments were prepared by blowing argon through the $CDCl_3$ solution. Elemental analyses were performed by the Microanalytical Service Laboratory of the Institute of Organic Chemistry, Bulgarian Academy of Sciences.

The following starting materials were used (commercially available or prepared according to the literature): (–)-menthone, Me_3SiCN, $BF_3{\cdot}OEt_2$, TBHP (3 M in *iso*-octane), $VO(acac)_2$ and Et_2Zn (1 M in hexane) (Fluka AG); $NaBH_3CN$ (Merck); $LiAlH_4$ (Aldrich); $CH_2{=}O$ (37% in water); $CH_2{=}CHMgBr$ and PhCH=CHMgBr were prepared from the correspond-



Scheme 3.

Table 1. Addition of Et_2Zn to benzaldehyde catalyzed by aminoalcohols **9**, **12**–**16** and **19**



Entry	Ligand	Time (h)	Yield[a] (%)	e.e.[b] (%)
1	**9**	120	79	9 (*S*)
2	**12**	120	67	40 (*S*)
3	**13**	51	89	3 (*S*)
4	**14**	98	69	19 (*S*)
5	**15**	72	72	0
6	**16**	22	98	77 (*S*)
7	**19**	48	87	40 (*S*)

[a] Yields of isolated 1-phenyl-1-propanol (after column chromatography).
[b] Determined by polarimetry based on the maximum value for the specific rotation of (*S*)-1-phenyl-1-propanol ($[\alpha]_D^{20}=-47$ (*c* 2.2, hexane) for 98% e.e. in the Fluka catalogue 1999/2000, p. 1142).

Table 2. ^{13}C NMR chemical shifts of compounds **2**, **4**, **7**–**9** and **12**–**19** ($CDCl_3$, 300 K, δ in ppm from TMS)[a]

Compound	**2**	**4**	**7**	**8a**	**9**[b]	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
No. C-atom													
C(1)	72.64	72.19	76.52	76.71	75.56	74.20	74.30	74.50	75.76	74.70	71.65	72.77	76.27
C(2)	49.18	51.90	49.09	49.83	48.46	51.58	52.33	50.01	53.24	50.47	47.44	47.54	46.13
C(3)	20.23	23.48	20.69	21.03	21.72	23.47	23.99	20.40	23.59	20.49	20.20	20.10	20.10
C(4)	34.10	33.94	35.05	35.09	36.36	35.05	34.90	35.16	35.06	35.38	34.93	35.07	34.97
C(5)	26.42	30.29	27.64	27.91	28.76	30.03	30.42	27.72	29.95	27.81	27.11	27.27	27.71
C(6)	47.65	48.86	48.98	49.30	45.83	45.71	46.69	46.93	46.99	47.38	46.71	46.67	41.31
C(7)	29.41	25.99	26.69	27.21	26.87	24.53	24.99	25.56	24.56	25.94	27.01	27.52	25.49
C(8)	18.66	17.37	18.38	18.66	18.64	19.54	19.86	17.99	19.40	18.02	17.90	17.99	18.09
C(9)	23.34	23.25	23.71	23.87	24.16	24.72	24.80	23.67	24.82	23.80	23.34	23.45	23.50
C(10)	21.45	21.35	22.14	22.25	23.01	22.46	22.12	22.48	22.41	22.67	22.07	22.17	22.71
C(11)	122.70	121.51	146.37	138.32	51.16	42.57	61.13	41.34	31.78	34.54	58.25	55.79	68.94
C(12)	–	–	111.01	126.55	–	–	47.94	37.41	36.95	55.22	44.52	68.91	55.05
C(13)	–	–	–	137.33	–	–	–	–	–	–	–	137.24	47.19
C(14)	–	–	–	126.29	–	–	–	–	–	–	–	125.43	11.50
C(15)	–	–	–	128.54	–	–	–	–	–	–	–	128.47	–
C(16)		–	–	127.10	–	–	–	–	–	–	–	128.02	–

[a] For the numbering of the menthane moiety see Scheme 1; the carbon atoms of the substituents were numbered continuously.
[b] In CD_3OD.

ing organic halides by known procedures;[19] anhydrous $CeCl_3$.[10a,10d,11b]

3.2. (1*S*,2*S*,5*R*)-1-Hydroxy-2-*iso*-propyl-5-methylcyclohex-1-yl-carbonitrile 2 and (1*R*,2*S*,5*R*)-1-hydroxy-2-*iso*-propyl-5-methylcyclohex-1-yl-carbonitrile 4

To **1** (0.90 g, 5.83 mmol) was added $BF_3{\cdot}OEt_2$ (0.83 g, 5.85 mmol) and Me_3SiCN (0.64 g, 6.45 mmol) at rt. The mixture was stirred for 1 h at rt then heated to 60°C and stirred for a further 0.5 h. After hydrolysis with 2N aqueous HCl, the mixture was extracted with Et_2O (3×15 mL). The organic extract was washed with 5% aq. $NaHCO_3$, H_2O and dried ($MgSO_4$). After evaporation of the solvent, the crude product (1.04 g, **2**:**3**:**4** = 20:11:69 by NMR) was chromatographed (∅ = 24 mm, *h* = 520 mm, 84 g silica gel, petroleum ether/Et_2O = 3:1) to give **3**, (0.13 g, 9%) **2**, (0.18 g, 17%), a mixed fraction (0.01 g) (**2**:**4** = 62:38 by NMR) and **4** (0.50 g, 47%). Compounds **2** and **4** were distilled (70°C, 0.001 Torr) and obtained as colorless crystals.

Data for 2: Mp 45–46°C. $[\alpha]_D^{20}=+1.9$ (*c* 1.02, $CHCl_3$). Anal. calcd for $C_{11}H_{19}NO$ (181.28): C, 72.88; H, 10.56; N, 7.73. Found: C, 72.95; H, 10.54; N, 7.58%. MS (CI: NH_3) *m*/*z* (rel. int.): 199 ($[M+18]^+$, 49), 181 ($[(M-H_2O)+18]^+$, 5), 172 ($[(M-HCN)+18]^+$, 100). ^1H NMR ($CDCl_3$, 300 K): δ 0.90–1.04 (m, 1H, H-4_{ax}), 0.91 (d, 3H, H-10, J = 6.4 Hz), 0.97 (d, 3H, H-8, J = 6.9 Hz), 1.03 (d, 3H, H-9, J = 6.9 Hz), 1.38–1.48 (m, 1H, H-2), 1.40–1.60 (m, 2H, H-3_{eq}, H-3_{ax}), 1.53 (t, 1H, H-6_{ax}, J = 12.0 Hz), 1.68–1.87 (m, 2H, H-4_{eq}, H-5), 2.11 (dt, 1H, H-6_{eq}, J = 13.7, 2.9 Hz), 2.23 (quintd, 1H, H-7, J = 6.9, 2.0 Hz), 2.62 (s, 1H, OH).

Data for 4: Mp 40–42°C. $[\alpha]_D^{20}=-12.9$ (*c* 1.05, $CHCl_3$). Anal. calcd for $C_{11}H_{19}NO$ (181.28): C, 72.88; H, 10.56; N, 7.73. Found: C, 72.61; H, 10.23; N, 7.44%. MS (CI:

NH_3) m/z (rel. int.): 199 ([M+18]$^+$, 32), 181 ([(M–H_2O)+18]$^+$, 3), 172 ([(M–HCN)+18]$^+$, 100). ^{1}H NMR ($CDCl_3$, 300 K): δ 0.87–0.95 (m, 1H, H-4$_{ax}$), 0.97 (d, 3H, H-10, J=6.4 Hz), 1.02 (d, 6H, H-8, H-9, J=7.1 Hz), 1.28–1.38 (m, 2H, H-2, H-3$_{ax}$), 1.29 (t, 1H, H-6$_{ax}$, J=12.2 Hz), 1.70–1.90 (m, 3H, H-3$_{eq}$, H-4$_{eq}$, H-5), 2.18 (dm, 1H, H-6$_{eq}$), 2.22 (quintd, 1H, H-7, J=7.0, 2.3 Hz), 2.45 (s, 1H, OH).

3.3. (1*R*,2*S*,5*R*)-1-Vinyl-2-*iso*-propyl-5-methylcyclohexan-1-ol 7

A mixture of **1** (0.64 g, 4.15 mmol) and anhydrous $CeCl_3$ (1.03 g, 4.18 mmol) in THF (20 mL) was stirred for 40 min at rt, and then cooled to −10°C. To this mixture was added a solution of CH_2=CH-MgBr in THF (0.86 M, 8 mL, 6.88 mmol). The resulting mixture was allowed to warm to rt and stirred at this temperature for 2 h. After hydrolysis (2N HCl), the mixture was extracted with petroleum ether (3×15 mL), the organic layer was washed with 5% aq. $NaHCO_3$, H_2O and dried (Na_2SO_4). After evaporation of the solvent, **7** was obtained (0.76 g, quantitative). For determination of $[\alpha]_D^{20}$, **7** was further purified by distillation (60°C, 0.001 Torr) to give a colorless liquid. $[\alpha]_D^{20}$=−19.2 (*c* 1.02, $CHCl_3$). Anal. calcd for $C_{12}H_{22}O$ (182.31): C, 79.06; H, 12.16. Found: C, 78.63; H, 11.86%. ^{1}H NMR ($CDCl_3$, 300 K): δ 0.72–0.97 (m, 1H, H-4$_{ax}$), 0.85 (d, 3H, H-8, J=6.9 Hz), 0.87 (d, 6H, H-9, H-10, J=7.1 Hz), 1.05–1.20 (m, 2H, H-2, H-6$_{ax}$), 1.23 (s, 1H, OH), 1.38–1.58 (m, 3H, H-3$_{eq}$, H-3$_{ax}$, H-6$_{eq}$), 1.60–1.90 (m, 1H, H-5), 1.60–1.80 (m, 1H, H-4$_{eq}$), 1.95 (quintd, 1H, H-7, J=6.9, 2.0 Hz), 5.07 (dd, 1H, H-12$_{cis}$, J=10.8, 1.5 Hz), 5.25 (dd, 1H, H-12$_{trans}$, J=17.4, 1.5 Hz), 5.86 (dd, 1H, H-11, J=17.4. 10.8 Hz).

3.4. (1*S*,2*S*,5*R*)-1-(*E*-2-Phenylethenyl)-2-*iso*-propyl-5-methylcyclohexan-1-ol 8a

A mixture of **1** (0.45 g, 2.92 mmol) and $CeCl_3$ (0.76 g, 3.08 mmol) in THF (15 mL) was stirred for 40 min at rt, then cooled to −10°C and treated with a solution of PhCH=CH-MgBr in THF (0.78 M, 7.5 mL, 5.85 mmol). The mixture was allowed to warm to rt and stirred at this temperature for 2 h. After hydrolysis (2N HCl), the mixture was extracted with petroleum ether (3×15 mL), the organic layer was washed with 5% aq. $NaHCO_3$, H_2O and dried (Na_2SO_4). After evaporation of the solvent, the crude product (0.99 g) was chromatographed (∅=17 mm, h=520 mm, 45 g silica gel, petroleum ether/Et_2O=10:1) to give a mixed fraction (0.12 g, **8a**:**8b**=65:35 by NMR) and **8a** (0.55 g, 73%). For the determination of $[\alpha]_D^{20}$, **8a** was further purified by distillation (70°C, 0.001 Torr) to give a colorless liquid. $[\alpha]_D^{20}$=−54.7 (*c* 1.04, $CHCl_3$). Anal. calcd for $C_{18}H_{26}O$ (258.40): C, 83.67; H, 10.14. Found: C, 82.44; H, 9.74%. MS (CI: NH_3) m/z (rel. int.): 258 [(M–H_2O)+18]$^+$, 15), 241 ([M–OH]$^{+\bullet}$, 100). ^{1}H NMR ($CDCl_3$, 300 K): δ 0.88 (d, 6H, H-8, H-9, J=6.9 Hz), 0.89 (d, 3H, H-10, J=6.4 Hz), 0.80–1.06 (m, 1H, H-4$_{ax}$), 1.16–1.31 (m, 2H, H-2, H-6$_{ax}$), 1.39 (s, 1H, OH), 1.51–1.63 (m, 2H, H-3$_{eq}$, H-6$_{eq}$), 1.54 (qd, 1H, H-3$_{ax}$, J=13.2, 3.4 Hz), 1.66–1.89 (m, 1H, H-5), 1.72–1.88 (m, 1H, H-4$_{eq}$), 2.00 (quintd, 1H, H-7, J=6.9, 2.1 Hz), 6.23 (d, 1H, H-11, J=16.1 Hz), 6.65 (d, 1H, H-12, J=16.1 Hz), 7.21 (tt, 1H, H-16, J=7.1, 1.9 Hz), 7.31 (tt, 2H, H-15, J=7.3, 1.6 Hz), 7.36–7.42 (m, 2H, H-14).

3.5. (1*S*,2*S*,5*R*)-1-Aminomethyl-2-*iso*-propyl-5-methylcyclohexan-1-ol 9

To a slurry of $LiAlH_4$ (0.42 g, 11.07 mmol) in Et_2O (7 mL) was added a solution of **2** (0.33 g, 1.82 mmol) in Et_2O (3 mL) at rt and the mixture was stirred for 1.5 h at the same temperature. It was hydrolyzed with 2N HCl and the acidic layer was washed with Et_2O (3×10 mL) and rendered alkaline by treatment with aq. NaOH. The alkaline layer was extracted (3×15 mL CH_2Cl_2). The evaporation of the Et_2O extract gave a mixture of **10** and **11** (0.15 g, 54% **10**:**11**=79:21 by NMR). Evaporation of the CH_2Cl_2 layer afforded **9** (0.13 g, 38%) as colorless crystals. Mp 22–23°C. $[\alpha]_D^{20}$=0.0 (*c* 1.04, MeOH). Anal. calcd for $C_{11}H_{23}NO$ (185.31): C, 71.30; H, 12.51; N, 7.56. Found: C, 67.95; H, 12.09; N, 6.51%. MS (CI: NH_3) m/z (rel. int.): 186 ([M+H]$^+$, 100), 168 ([M–OH]$^{+\bullet}$, 2). ^{1}H NMR (CD_3OD, 300 K): δ 0.75–0.90 (m, 1H, H-4$_{ax}$), 0.90 (d, 3H, H-8, J=6.9 Hz), 0.90 (d, 3H, H-10, J=6.1 Hz), 0.92 (d, 3H, H-9, J=6.9 Hz), 1.00 (dd, 1H, H-6$_{ax}$, J=13.3, 12.1 Hz), 1.10–1.20 (m, 1H, H-2), 1.43–1.58 (m, 2H, H-3$_{eq}$, H-3$_{ax}$), 1.61 (ddd, 1H, H-6$_{eq}$, J=13.2, 3.6, 2.4 Hz), 1.63–1.84 (m, 1H, H-5), 1.68–1.82 (m, 1H, H-4$_{eq}$), 2.04 (quintd, 1H, H-7, J=6.9, 1.9 Hz), 2.61 (d, 1H, H$_a$-11, J=13.2 Hz), 2.74 (d, 1H, H$_b$-11, J=13.2 Hz).

3.6. (1*R*,2*S*,5*R*)-1-Aminomethyl-2-*iso*-propyl-5-methylcyclohexan-1-ol 12

To a slurry of $LiAlH_4$ (0.70 g, 18.45 mmol) in Et_2O (7 mL) was added **4** (0.57 g, 3.15 mmol) in Et_2O (3 mL) at rt and the mixture was stirred for 1.5 h. The mixture was hydrolyzed with 2N HCl and the acidic layer was extracted with Et_2O (3×10 mL) and rendered alkaline by treatment with aq. NaOH. The alkaline layer was extracted with CH_2Cl_2 (3×15 mL) and dried ($MgSO_4$). Evaporation of the Et_2O extract gave of a **10**/**11**-mixture (0.11 g, 22%, **10**/**11**=76:24 by NMR). Evaporation of the CH_2Cl_2 layer afforded **12** as colorless crystals (0.34 g, 59%). Mp 38–40°C. $[\alpha]_D^{20}$=−26.2 (*c* 1.10, MeOH). Anal. calcd for $C_{11}H_{23}NO$ (185.31): C, 71.30; H, 12.51; N, 7.56. Found: C, 66.68; H, 11.21; N, 6.13%. MS (CI: NH_3) m/z (rel. int.): 186 ([M+H]$^+$, 100). ^{1}H NMR ($CDCl_3$, 300 K): δ 0.77–0.97 (m, 1H, H-6$_{ax}$), 0.79 (d, 3H, H-8, J=6.9 Hz), 0.85–1.00 (m, 1H, H-4$_{ax}$), 0.89 (d, 3H, H-10, J=6.6 Hz), 0.96 (d, 3H, H-9, J=6.9 Hz), 1.11 (qd, 1H, H-3$_{ax}$, J=12.9, 3.4 Hz), 1.27–1.49 (m, 1H, H-5), 1.33 (ddd, 1H, H-2, J=13.0, 3.5, 2.0 Hz), 1.61 (dq, 1H, H-3$_{eq}$, J=12.8, 3.3 Hz), 1.72 (dm, 1H, H-4$_{eq}$, J=12.7 Hz), 1.85 (dt, 1H, H-6$_{eq}$, J=13.2, 2.7 Hz), 2.13 (quintd, 1H, H-7, J=6.9, 2.0 Hz), 2.70 (dd, 1H, H-11, J=13.0, 1.2 Hz), 2.87 (d, 1H, H-11′, J=13.0 Hz).

3.7. (1*R*,2*S*,5*R*)-1-*N*,*N*-Dimethylaminomethyl-2-*iso*-propyl-5-methylcyclohexan-1-ol 13

To a mixture of **12** (0.097 g, 0.524 mmol) in MeCN (2 mL) and aq. CH_2O (37 wt%, 0.35 mL) at rt was added

$NaBH_3CN$ (0.070 g, 1.114 mmol). The mixture was stirred for 25 min and glacial acetic acid was added to neutralize the reaction (pH paper). The mixture was stirred for an additional 2 h at rt, then acidified (2N HCl), washed with CH_2Cl_2 (3×10 mL), alkalized (aq. NaOH), extracted with CH_2Cl_2 (3×7 mL) and the organic layer dried ($MgSO_4$). Evaporation of the organic extract afforded **13** as colorless liquid (0.027 g, 24%). $[\alpha]_D^{20}=-41.4$ (*c* 1.14, $CHCl_3$). Anal. calcd for $C_{13}H_{27}NO$ (213.36): C, 73.18; H, 12.75; N, 6.56. Found: C, 73.95; H, 12.51; N, 6.15%. MS (EI:) *m*/*z* (rel. int.): 213 (M^+, 21), 198 (11), 170 (5), 154 (9), 137 (11), 128 (67), 111 (9), 95 (28), 81 (34), 69 (34), 60 (59), 58 (C_3H_8N, 100), 55 (49). ^1H NMR ($CDCl_3$, 300 K): δ 0.80 (d, 3H, H-8, $J=7.1$ Hz), 0.82–0.93 (m, 1H, H-4_{ax}), 0.85–0.97 (m, 1H, H-3_{ax}), 0.92 (d, 3H, H-10, $J=6.5$ Hz), 0.98 (d, 3H, H-9, $J=6.8$ Hz), 1.03 (t, 1H, H-6_{ax}, $J=13.6$ Hz), 1.25 (s, 1H, OH), 1.30 (dt, 1H, H-2, $J=12.9$, 3.1 Hz), 1.37–1.47 (m, 1H, H-5), 1.64 (dq, 1H, H-3_{eq}, $J=13.1$, 3.3 Hz), 1.73 (dm, 1H, H-4_{eq}, $J=12.9$ Hz), 2.10 (quintd, 1H, H-7, $J=6.9$, 2.5 Hz), 2.19 (d, 1H, H-6_{eq}, $J=13.6$ Hz), 2.59 (s, 6H, NMe_2), 2.69 (d, 1H, H_a-11, $J=13.1$ Hz), 2.81 (d, 1H, H_b-11, $J=13.1$ Hz).

3.8. (1*R*,2*S*,5*R*)-1-(2′-Aminoethyl)-2-*iso*-propyl-5-methylcyclohexan-1-ol 14

To $LiAlH_4$ (0.30 g, 7.91 mmol) in Et_2O (5 mL) was added **5** (0.40 g, 2.05 mmol, 92% d.e. by NMR) in Et_2O (5 mL) at rt and the mixture was stirred for 1.5 h. The mixture was hydrolyzed with 2N HCl, the acidic layer was washed with Et_2O (3×10 mL) and rendered alkaline with aq. NaOH. The alkaline layer was extracted with CH_2Cl_2 (3×15 mL) and the extract dried ($MgSO_4$). Evaporation of the solvent afforded **14** (0.30 g, 73%, 92% d.e. by NMR) as a colorless glass-like solid. $[\alpha]_D^{20}=-12.6$ (*c* 1.01, $CHCl_3$). Anal. calcd for $C_{12}H_{25}NO$ (199.34): C, 72.30; H, 12.64; N, 7.03; Found: C, 71.10; H, 12.40; N, 6.88%. MS (EI:) *m*/*z* (rel. int.): 199 (M^+, 19), 184 (9), 164 (12), 152 (61), 138 (23), 137 (23), 114 (100), 109 (29), 96 (28), 95 (40), 87 (54), 85 (72), 81 (29), 69 (33), 55 (42). ^1H NMR ($CDCl_3$, 300 K): δ 0.72–0.97 (m, 1H, H-4_{ax}), 0.77–0.94 (m, 1H, H-6_{ax}), 0.85–1.02 (m, 1H, H-2), 0.87 (d, 3H, H-10, $J=6.1$ Hz), 0.89 (d, 3H, H-9, $J=7.1$ Hz), 0.92 (d, 3H, H-8, $J=6.9$ Hz), 1.32–1.47 (m, 1H, H_a-11), 1.37–1.55 (m, 2H, H-3_{eq}, H-3_{ax}), 1.67–1.82 (m, 1H, H-4_{eq}), 1.67–1.88 (m, 1H, H-5), 1.68–1.80 (m, 1H, H-6_{eq}), 1.84–1.99 (m, 1H, H_b-11), 2.16 (septd, 1H, H-7, $J=6.9$, 1.9 Hz), 2.90–3.00 (m, 2H, H-12).

3.9. (1*S*,2*S*,5*R*)-1-(2′-Aminoethyl)-2-*iso*-propyl-5-methylcyclohexan-1-ol 15

To a suspension of $LiAlH_4$ (0.28 g, 7.38 mmol) in Et_2O (4 mL) was added a solution of **6** (0.19 g, 0.97 mmol) in Et_2O (4 mL) at rt and the mixture was stirred for 2 h. It was hydrolyzed with 2N HCl, the acidic layer was washed (3×10 mL Et_2O) and alkalized with aq. NaOH. The alkaline layer was extracted (3×15 mL CH_2Cl_2) and the organic extract was dried ($MgSO_4$). Evaporation of the solvent afforded **15** as a colorless liquid (0.16 g, 84%). $[\alpha]_D^{20}=-17.4$ (*c* 1.09, $CHCl_3$). Anal. calcd for $C_{12}H_{25}NO$ (199.34): C, 72.30; H, 12.64; N, 17.03. Found: C, 70.38; H, 11.62; N, 5.78%. MS (CI: NH_3) *m*/*z* (rel. int.): 399 ($[2M+H]^+$, 28), 200 ($[M+H]^+$, 100). ^1H NMR ($CDCl_3$, 300 K): δ 0.82 (d, 3H, H-8, $J=6.8$ Hz), 0.88 (d, 3H, H-10, $J=6.4$ Hz), 0.90–1.05 (m, 1H, H-6_{ax}), 0.97 (d, 3H, H-9, $J=6.9$ Hz), 1.05–1.22 (m, 2H, H-2, H-3_{ax}), 1.20–1.40 (m, 1H, H-5), 1.53–1.65 (m, 1H, H-3_{eq}), 1.64–1.75 (m, 2H, H-4_{eq}, H-11), 1.95 (d, 1H, H-6_{eq}, $J=13.0$ Hz), 2.21 (sept, 1H, H-7, $J=6.8$ Hz), 2.85–3.12 (m, 2H, H-12).

3.10. (1*R*,2*S*,5*R*)-1-(2′-*N*,*N*-Dimethylaminoethyl)-2-*iso*-propyl-5-methylcyclohexan-1-ol 16

To a mixture of **14** (0.16 g, 0.80 mmol, 92% d.e.) in MeCN (4 mL) and aq. CH_2O (37 wt%, 0.50 mL) were added 0.10 g (1.59 mmol) solid $NaBH_3CN$ at rt. The mixture was stirred for 25 min and glacial acetic acid was added to neutral reaction of pH paper. The mixture was stirred at rt for an additional 2 h, then acidified (2N HCl), washed (3×10 mL CH_2Cl_2) and rendered alkaline by treatment with aq. NaOH. The mixture was extracted with CH_2Cl_2 (3×7 mL) and the organic layer was dried ($MgSO_4$). Evaporation of the solvent afforded **16** (0.07 g, 39%, 92% d.e. by NMR) as colorless liquid. $[\alpha]_D^{20}=-17.2$ (*c* 1.00, $CHCl_3$). Anal. calcd for $C_{14}H_{29}NO$ (227.39): C, 73.95; H, 12.85; N, 6.16. Found: C, 73.48; H, 11.13; N, 5.70%. MS (EI:) *m*/*z* (rel. int.): 226 ($[M-H]^{+\bullet}$, 49), 210 ($[M-OH]^{+\bullet}$, 11), 182 (7), 168 (7), 154 (6), 140 (26), 126 (13), 109 (17), 101 (57), 95 (20), 81 (20), 74 (63), 69 (31), 58 (C_3H_8N, 100), 57 (46), 55 (56). ^1H NMR ($CDCl_3$, 300 K): δ 0.70–0.90 (m, 1H, H-4_{ax}), 0.79 (t, 1H, H-6_{ax}, $J=13.0$ Hz), 0.85–0.98 (m, 1H, H-2), 0.87 (d, 3H, H-10, $J=6.1$ Hz), 0.90 (d, 3H, H-9, $J=6.9$ Hz), 0.94 (d, 3H, H-8, $J=6.9$ Hz), 1.05–1.20 (m, 1H, H_a-11), 1.39–1.59 (m, 2H, H-3_{eq}, H-3_{ax}), 1.69–1.80 (m, 2H, H-4_{eq}, H-6_{eq}), 1.70–1.88 (m, 1H, H-5), 2.08–2.23 (m, 1H, H_b-11), 2.10–2.20 (m, 1H, H-7), 2.13–2.29 (m, 1H, H_a-12), 2.25 (s, 6H, NMe_2), 2.73–2.90 (m, 1H, H_b-12).

3.11. (1*S*,2*S*,5*R*)-1-Epoxyethyl-2-*iso*-propyl-5-methylcyclohexan-1-ol 17

To a mixture of **7** (0.930 g, 5.10 mmol) and $VO(acac)_2$ (0.027 g, 0.10 mmol) in CH_2Cl_2 (40 mL) at rt was added a solution of TBHP in *iso*-octane (3 M, 4 mL, 12.00 mmol). The mixture was stirred for 27 h at rt, washed with a solution of NaCl (1 g) and NaOH (3 g) in H_2O (10 mL) then further washed with H_2O, and the organic layer dried ($MgSO_4$). After evaporation of the solvent, the crude product (0.980 g) was chromatographed ($\varnothing=24$ mm, $h=520$ mm, 87 g silica gel, petroleum ether/$Et_2O=2:1$) to give **17** as colorless crystals (0.820 g, 81%) and its diastereoisomer (0.008 g, <1%). For determination of $[\alpha]_D^{20}$, **17** was additionally purified by distillation (70°C, 0.001 Torr). Mp 66–67°C. $[\alpha]_D^{20}=-4.8$ (*c* 0.99, $CHCl_3$). Anal. calcd for $C_{12}H_{22}O_2$ (198.30): C, 72.68; H, 11.18. Found: C, 72.55; H, 11.09%. MS (CI: NH_3) *m*/*z* (rel. int.): 216 ($[M+18]^+$, 100), 199 ($[M+H]^+$, 19), 181 (31), 163 (28), 137 (9). ^1H NMR ($CDCl_3$, 300 K): $\delta=0.87$ (d, 3H, H-8, $J=6.9$ Hz), 0.89 (d, 3H, H-10, $J=6.1$ Hz), 0.91 (d, 3H, H-9,

$J=6.9$ Hz), 1.10 (d, 1H, OH, $J=1.5$ Hz), 1.13 (dd, 1H, H-6_{ax}, $J=13.3$, 12.1 Hz), 1.21–1.32 (m, 1H, H-2), 1.43–1.60 (m, 2H, H-3_{eq}, H-3_{ax}), 1.67 (ddd, 1H, H-6_{eq}, $J=13.5$, 3.3, 2.5 Hz), 1.72–1.87 (m, 2H, H-4_{eq}, H-5), 2.01 (septd, 1H, H-7, $J=6.9$, 2.1 Hz), 2.76–2.84 (m, 2H, H-11, H_a-12), 2.95 (dd, 1H, H_b-12, $J=4.8$, 3.3 Hz).

3.12. (1*S*,2*S*,5*R*,1′*R*,2′*S*)-1-(2′-Phenylepoxyethyl)-2-*iso*-propyl-5-methylcyclohexan-1-ol 18

To a mixture of **8a** (0.420 g, 1.63 mmol) and $VO(acac)_2$ (0.011 g, 0.04 mmol) in CH_2Cl_2 (17 mL) were added at rt a solution of TBHP in *iso*-octane (3 M, 1.3 mL, 3.90 mmol). The mixture was stirred for 47 h at rt, washed with a solution of NaCl (1 g) and NaOH (3 g) in H_2O (10 mL), then with H_2O, and the organic layer dried ($MgSO_4$). After evaporation of the solvent, the crude product (0.440 g, 82% d.e. by NMR) was chromatographed ($\varnothing=13$ mm, $h=430$ mm, 26 g silica gel, petroleum ether/$Et_2O=2:1$) to give **18** (0.340 g, 76%) as a single diastereoisomer (colorless crystals). For determination of $[\alpha]_D^{20}$, **18** was further purified by distillation (70°C, 0.001 Torr). Mp 109–112°C. $[\alpha]_D^{20}=-31.2$ (*c* 1.06, $CHCl_3$). Anal. calcd for $C_{18}H_{26}O_2$ (274.40): C, 78.79; H, 9.55. Found: C, 78.49; H, 9.62%. MS (CI: NH_3) *m*/*z* (rel. int.): 292 ($[M+18]^+$, 6), 257 ($[M-OH]^{+\bullet}$, 100). ^1H NMR ($CDCl_3$, 300 K): δ 0.78–0.98 (m, 1H, H-4_{ax}), 0.84 (d, 3H, H-9, $J=6.9$ Hz), 0.92 (d, 3H, H-10, $J=6.4$ Hz), 0.97 (d, 3H, H-8, $J=6.8$ Hz), 1.16 (dd, 1H, H-6_{ax}, $J=13.9$, 13.0 Hz), 1.21–1.30 (m, 1H, H-2), 1.31 (d, 1H, OH, $J=1.2$ Hz), 1.50–1.63 (m, 2H, H-3_{eq}, H-3_{ax}), 1.71–1.88 (m, 3H, H-4_{eq}, H-5, H-6_{eq}), 1.98 (quintd, 1H, H-7, $J=6.9$, 2.2 Hz), 2.79 (d, 1H, H-12, $J=2.2$ Hz), 4.06 (d, 1H, H-11, $J=2.2$ Hz), 7.25–7.41 (m, 5H, Ph).

3.13. (1*S*,2*S*,5*R*)-1-(2′-*N*,*N*-Diethylamino-1′-hydroxyethyl)-2-*iso*-propyl-5-methylcyclohexan-1-ol 19

To a mixture of **17** (0.72 g, 3.63 mmol) and $LiClO_4$ (1.55 g, 14.57 mmol) in acetonitrile (3 mL) was added Et_2NH (0.57 g, 7.79 mmol). The mixture was heated at 60°C for 4 h and the solvent was evaporated. After the residue was acidified with 2N HCl, the acidic phase was washed with CH_2Cl_2 (3×10 mL), rendered alkaline by treatment with aq. NaOH, extracted with CH_2Cl_2 (3×10 mL) and the organic layer was dried (Na_2SO_4). Evaporation of the solvent afforded **19** as yellowish highly hygroscopic crystals (0.19 g, 19%). $[\alpha]_D^{20}=0.0$ (*c* 1.03, $CHCl_3$). MS (CI: NH_3) *m*/*z* (rel. int.): 272 ($[M+H]^+$, 100). ^1H NMR ($CDCl_3$, 300 K): δ 0.77–0.90 (m, 1H, H-4_{ax}), 0.88 (d, 3H, H-10, $J=6.6$ Hz), 0.91 (d, 6H, H-8, H-9, $J=7.1$ Hz), 1.05 (t, 6H, H-14, $J=7.2$ Hz), 1.02–1.17 (m, 1H, H-6_{ax}), 1.30–1.50 (m, 1H, H-2), 1.35–1.55 (m, 2H, H-3_{eq}, H-3_{ax}), 1.40–1.50 (m, 1H, H-6_{eq}), 1.67–1.80 (m, 1H, H-4_{eq}), 1.70–1.87 (m, 1H, H-5), 2.26 (quintd, 1H, H-7, $J=6.9$, 1.5 Hz), 2.52 (dd, 1H, H_a-12, $J=12.5$, 7.8 Hz), 2.61 (qd, 4H, H-13, $J=7.2$, 0.9 Hz), 2.70 (dd, 1H, H_b-12, $J=12.7$, 6.6 Hz), 3.91 (t, 1H, H-11, $J=7.2$ Hz).

3.14. X-Ray crystallographic details for compound 18

$C_{18}H_{26}O_2$, $M_r=274.40$, monoclinic, space group $P2_1$, $a=11.7748(6)$, $b=5.8362(4)$, $c=12.9741(9)$ Å, $\beta=113.262(2)°$, $V=819.10(9)$ Å^3, $Z=2$, $D_c=1.112$ Mg m^{-3}, μ(Mo Kα)$=0.0703$ mm^{-1}, $F(000)=300$, $T=160(1)$ K, colorless prism, dimensions: 0.13×0.25×0.28 mm, Nonius KappaCCD diffractometer, Mo Kα radiation, $\lambda=0.71073$ Å, $2\theta_{max}=50°$, 10705 measured reflections of which 2782 were unique. The intensities were corrected for Lorentz and polarization effects, but not for absorption. Structure solution by direct methods using SHELXS-97[20] and refined on F by full-matrix least-squares methods using teXsan,[21] non-H atoms refined anisotropically, hydroxy H-atom refined isotropically, all other H-atoms fixed in calculated positions. The refinement of 185 parameters using 2460 observed reflections with $I>2\sigma(I)$ gave $R=0.060$, $wR=0.071$, $S=3.300$, weights: $[\sigma^2(F_o)+(0.0075F_o)^2]^{-1}$, max and min $\Delta\rho=0.18$; −0.17 e Å^{-3}. Crystallographic data (excluding structure factors) for the structures of **18** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC-161028. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033; email: deposit@ccdc.cam.ac.uk).

Acknowledgements

Support of this work by the Bulgarian Fund for Scientific Research (project X-711) is gratefully acknowledged. The authors would like to thank Mr. N. Bild, Institute of Organic Chemistry, University of Zurich, for recording the mass spectra and for very helpful hints concerning the mass spectrometry.

References

1. For reviews, see: (a) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771–806; (b) Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807–832; (c) Blaser, H.-U. *Chem. Rev.* **1992**, *92*, 935–952; (d) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007–1019; (e) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021–1050; (f) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117–2188; (g) Fenwick, D. R.; Kagan, H. B. *Top. Stereochem.* **1999**, *22*, 257–296; (h) Shibasaki, M.; Sasai, H. *Top. Stereochem.* **1999**, *22*, 201–225; (i) Jorgensen, K. A.; Johansen, M.; Yao, S.; Andrian, H.; Thorhange, J. *Acc. Chem. Res.* **1999**, *32*, 605–613; (j) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159–2231; (k) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824.
2. (a) Rosini, C.; Franzini, L.; Raffaeli, A.; Salvadori, P. *Synthesis* **1992**, 503–517; (b) Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Synlett* **1992**, 255–261; (c) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345–350; (d) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137–1141.
3. The theme *Diastereoselection* is treated within several review articles published in *Chem. Rev.* **1999**, *92*, No. 5.
4. (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; Chapter 5; (b) Noyori, R.;

Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69; (c) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–956; (d) Avalos, M.; Babiano, R.; Cintas, P.; Jimenez, J. L.; Palacios, J. C. *Tetrahedron: Asymmetry* **1997**, *8*, 2997–3017.

5. (a) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071–6072; (b) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M. *Pure Appl. Chem.* **1988**, *60*, 1597–1606; (c) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028–4036; (d) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M.; Oguni, N.; Hayashi, M.; Kaneko, T.; Matsuda, Y. *J. Organomet. Chem.* **1990**, *382*, 19–37; (e) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832–4842; (f) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327–6335; (g) Kitamura, M.; Yamakawa, M.; Oka, H.; Suga, S.; Noyori, R. *Chem. Eur. J.* **1996**, *2*, 1173–1181; (h) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800–9809.
6. (a) Muchow, G.; Vannoorenberghe, Y.; Buono, G. *Tetrahedron Lett.* **1987**, *28*, 6163–6166; (b) Oppolzer, W.:; Radinov, R. N. *Tetrahedron Lett.* **1988**, *29*, 5645–5648; (c) Cicchi, S.; Crea, S.; Goti, A.; Brandi, A. *Tetrahedron: Asymmetry* **1997**, *8*, 293–301.
7. Genov, M.; Kostova, K.; Dimitrov, V. *Tetrahedron: Asymmetry* **1997**, *8*, 1869–1876.
8. Genov, M.; Dimitrov, V.; Ivanova, V. *Tetrahedron: Asymmetry* **1997**, *8*, 3703–3706.
9. (a) Hanyu, N.; Aoki, T.; Mino, T.; Sakamoto, M.; Fujita, T. *Tetrahedron: Asymmetry* **2000**, *11*, 2971–2979; (b) Hanyu, N.; Aoki, T.; Mino, T.; Sakamoto, M.; Fujita, T. *Tetrahedron: Asymmetry* **2000**, *11*, 4127–4136; (c) Hanyu, N.; Mino, T.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* **2000**, *41*, 4587–4590; (d) Knollmüller, M.; Ferencic, M.; Gärtner, P. *Tetrahedron: Asymmetry* **1999**, *10*, 3969–3975.
10. (a) Dimitrov, V.; Bratovanov, S.; Simova, S.; Kosatova, K. *Tetrahedron Lett.* **1994**, *35*, 6713–6716; (b) Dimitrov, V.; Simova, S.; Kostova, K. *Tetrahedron* **1996**, *52*, 1699–1706; (c) Dimitrov, V.; Philipova, I.; Simova, S. *Tetrahedron: Asymmetry* **1996**, *7*, 1493–1500; (d) Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett.* **1996**, *37*, 6787–6790; (e) Philipova, I.; Dimitrov, V.; Simova, S. *Tetrahedron: Asymmetry* **1999**, *10*, 913–921; (f) Philipova, I.; Dimitrov, V.; Simova, S. *Tetrahedron: Asymmetry* **1999**, *10*, 1381–1391; (g) Dimitrov, V.; Dobrikov, G; Genov, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1323–1329.
11. (a) Dimitrov, V.; Panev, S. *Tetrahedron: Asymmetry* **2000**, *11*, 1513–1516; (b) Panev, S.; Dimitrov, V. *Tetrahedron: Asymmetry* **2000**, *11*, 1517–1526.
12. Watanabe, S.; Suga, K.; Suematsu, Y.; Suzuki, T. *Aust. J. Chem.* **1968**, *21*, 531–536.
13. Chillous, S. E.; Hart, D. J.; Hutchinson, D. K. *J. Org. Chem.* **1982**, *47*, 5418–5420.
14. Spino, C.; Beaulieu, C. *J. Am. Chem. Soc.* **1998**, *120*, 11832–11833.
15. Johnson, C. K. ORTEPII. Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, TN, USA, 1976.
16. (a) Hoveyda, A. H. *Chem. Rev.* **1993**, *93*, 1307–1370; (b) Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690–7692.
17. (a) Chini, M.; Crotti, P.; Macchia, F. *Tetrahedron Lett.* **1990**, *31*, 4661–4664; (b) Chini, M.; Crotti, P.; Macchia, F. *J. Org. Chem.* **1991**, *56*, 5939–5942; (c) Smith, J. G. *Synthesis* **1984**, 629–656.
18. Simova, S. *Magn. Reson. Chem.* **1998**, *36*, 505–510.
19. *Houben-Weyl Methoden der organishen Chemie*; Müller, E., Ed. Organo-magnesium-Verbindungen. Georg Thieme Verlag: Stuttgart, 1973; Vol. 13/2a, p. 47.
20. Sheldrick, G. M. *SHELXS-97. Program for the Solution of Crystal Structures*; University of Göttingen: Germany, 1997.
21. teXsan. Single Crystal Structure Analysis Software, Version 1.10. Molecular Structure Corporation: The Woodlands, TX, USA, 1999.