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Chiral β- and γ-aminoalcohols derived from (+)-camphor and (−)-fenchone as catalysts for the enantioselective addition of diethylzinc to benzaldehyde

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Abstract—The addition of Me_3SiCN and $LiCH_2CN$ to (+)-camphor and (−)-fenchone, respectively, followed by reduction leads to chiral β- and γ-aminoalcohols. The enantioselectivities realized using these aminoalcohols as ligands in the addition of Et_2Zn to benzaldehyde were lower than those obtained using the corresponding δ-aminoalcohols.

1. Introduction

The enantioselective addition of dialkylzinc compounds to aldehydes catalyzed by chiral aminoalcohols is an important synthetic method for the preparation of enantiomerically pure or enantiomerically enriched secondary alcohols and has been of considerable interest over recent years.[1–3] Since Noyori et al. demonstrated the high efficiency of (−)-3-*exo*-dimethylamino isoborneol as catalyst,[4] β-aminoalcohols have mainly been prepared and applied as catalysts. However, since γ- and δ-aminoalcohol ligands were found to induce a high degree of enantioselectivity in the addition of R_2Zn compounds to aldehydes,[5–7] there has been increasing interest in their synthesis and application.

Herein, we present the results of investigations into the preparation and application as ligands of chiral camphor and fenchone derived β- and γ-aminoalcohols, and compare their catalytic activity with the reported results using the corresponding δ-aminoalcohols.[6]

2. Results and discussion

For the preparation of β- and γ-aminoalcohols, Me_3SiCN and $LiCH_2CN$[8] were added to (+)-camphor **1** and (−)-fenchone **2**, respectively (Scheme 1). The addition of Me_3SiCN to **1** and **2** required activation of the ketones with 20 mol% of $BF_3{\cdot}OEt_2$, otherwise addition did not occur. The use of a solvent (Et_2O, CH_2Cl_2) resulted in low yields and in order to obtain good conversion of the ketones it was necessary to complete the reactions in the absence of a solvent. However, after hydrolytic work-up, the main components in the reaction mixtures were the silyl ethers **5** and **6** for camphor, and **8** for fenchone. This was reflected in the isolation of the desired compounds **3**, **4** and **7** in low yields. Furthermore, although *endo*-attack of nucleophilic reagents to camphor is preferred in most of the cases, the addition of Me_3SiCN occurred with the formation of significant amounts of the *exo*-addition products (**4** and **6**, Scheme 1). In the case of fenchone, only the expected *exo*-addition was observed.

In attempts to hydrolyze the silyl ethers **5**, **6** and **8**, no reaction occurred with 2N aqueous HCl in THF and 40% aqueous HF in MeCN, and the use of *n*-$Bu_4NF{\cdot}3H_2O$ in THF led to the quantitative back formation of the corresponding ketones. Derivatives **5** and **6** were not separated into individual diastereoisomers.

The preparation of compounds **9** and **10** was effected by addition of $LiCH_2CN$ to the $CeCl_3$ activated[9] ketones **1** and **2** (Scheme 1). The best yields were observed when the ketone/$CeCl_3$/THF mixture, after stirring at room temperature for 1 h, was cooled to −78°C and solid $LiCH_2CN$ was added rapidly.

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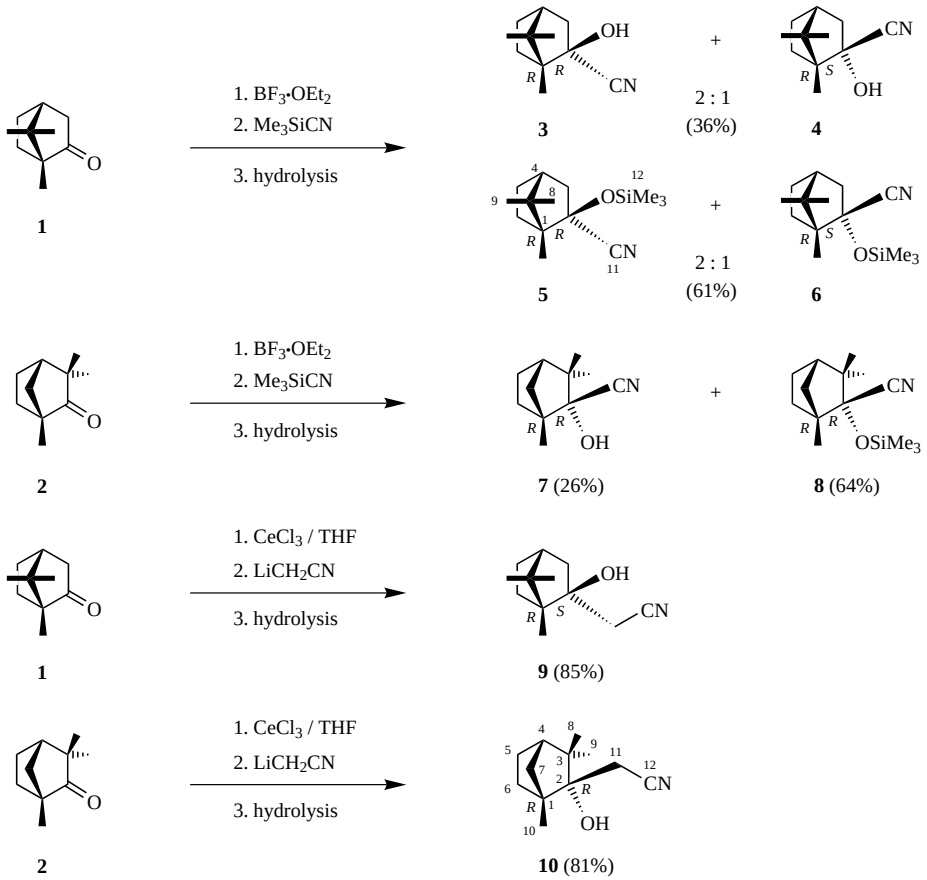
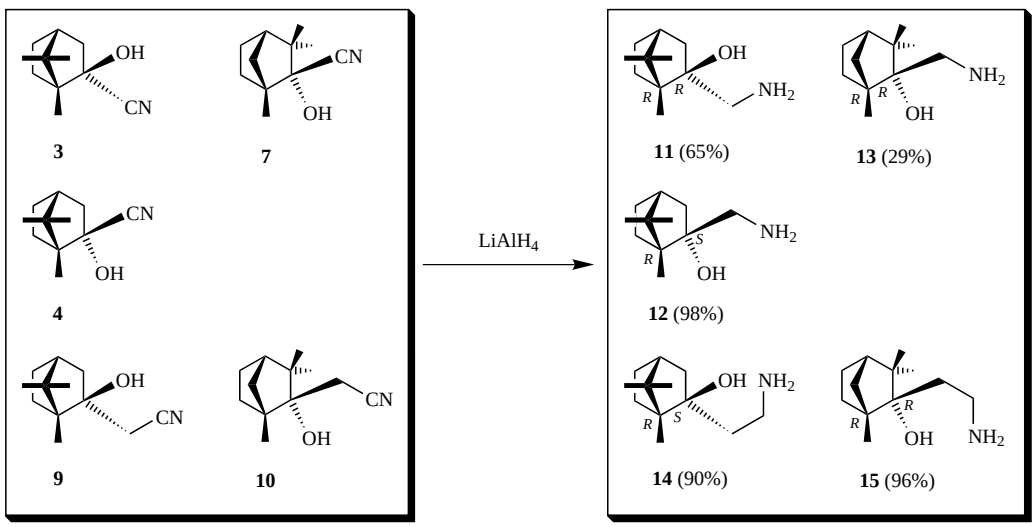


Scheme 1.

For the preparation of the β-aminoalcohols **11**–**13**, compounds **3**, **4** and **7** were reduced with $LiAlH_4$. In contrast to the excellent yield of **12**, aminoalcohols **11** and **13** were obtained in moderate to low yields (Scheme 2). In both of the latter cases, the formation of side products (isoborneol, borneol and fenchol) was observed, indicating the in situ formation of camphor and fenchone, respectively, which were then reduced. The cyanomethyl products **9** and **10** were transformed into the γ-aminoalcohols **14** and **15** in very good yields. Whereas **11**–**13** and **15** are colorless solids and are stable for several weeks, compound **14** decomposed to a red–brown liquid within hours (which led to incorrect elemental analysis).



Scheme 2.

The aminoalcohols **11**–**15** were applied as catalysts (3 mol%) for the enantioselective addition of Et_2Zn to benzaldehyde (Table 1). The addition reactions were carried out in hexane with a 1 M solution of Et_2Zn in hexane according to the published procedure.[6] The yields of the isolated 1-phenyl-1-propanol were excellent. However, the observed enantioselectivities were low and, in the case of **12**, no asymmetric induction was realized. This low enantioselectivity may be due to the formation of a strong covalent N–Zn bond within the catalyst complex and the possibility for an amino group to block two Zn atoms via protolysis of the ethyl groups. The *N*-dimethylamino δ-aminoalcohols **16** and **17** afforded better enantioselectivities.

The unambiguous assignment of the proton and carbon-13 spectra of compounds **3**–**15** (Table 2 and Experimental) was made on the basis of DEPT, HSQC[10] and NOESY experiments.

In conclusion, the obtained β- and γ-aminoalcohols induced low enantioselectivity for the addition of Et_2Zn to benzaldehyde. However, the synthesized enantiomerically pure derivatives may also find other applications in synthetic chemistry. The preparation of similar derivatives bearing a dialkylamino group using another synthetic strategy is in progress.

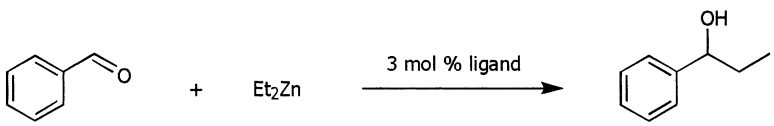
3. Experimental

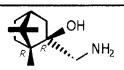
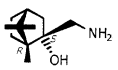
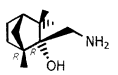
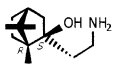
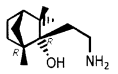
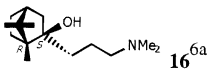
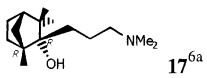
3.1. General methods and starting materials

The reactions were carried out in flame-dried Schlenk flasks under an argon atmosphere. THF and Et_2O were distilled over sodium/benzophenone. Hexane was distilled over $Na[Et_4Al]$. Thin layer chromatography (TLC): aluminum sheets pre-coated with silica gel 60 F_{254} (Merck). Column chromatography was carried out at normal pressure, using silica gel 60 (0.063–0.200 mm, Merck).

Melting points were obtained using a Kofler block apparatus (uncorrected). Optical rotation ($[\alpha]_D^{20}$) measurements were obtained using a Perkin–Elmer 241 polarimeter. Mass spectra (MS) were recorded on 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.

Table 1. Addition of Et_2Zn to benzaldehyde catalyzed by aminoalcohols **11**–**17**



Entry	Ligand	Time (h)	Yield[a] (%)	E.e.[b] (%)
1	 **11**	21	83	26 (*S*)
2	 **12**	48	99	0
3	 **13**	69	88	37 (*S*)
4	 **14**	40	86	9 (*R*)
5	 **15**	48	80	28 (*R*)
6	 **16**[6a]	27	99	56 (*S*)
7	 **17**[6a]	27	99	58 (*R*)

[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 Fluka catalogue 1999/2000, p. 1142).

Table 2. ^{13}C NMR chemical shifts of compounds **3**–**15** ($CDCl_3$, 300 K, δ in ppm from TMS)[a]

No. C atom	Compound												
	3	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
C(1)	53.36	54.56	54.00	55.30	53.25	54.16	52.40	52.20	51.21	52.20	51.56	52.24	52.79
C(2)	77.99	76.07	78.42	76.78	82.45	83.54	78.95	79.81	78.64	78.66	78.06	82.20	81.98
C(3)	46.32	44.92	48.56	45.56	43.17	43.44	46.26	44.06	45.00	43.27	43.63	47.21	44.53
C(4)	44.82	44.84	45.01	44.91	48.21	48.42	44.79	49.23	45.00	44.76	49.59	45.15	50.40
C(5)	26.50	26.87	26.40	26.90	25.49	25.67	26.65	24.76	27.16	26.78	25.46	27.12	25.12
C(6)	32.17	27.20	31.56	27.30	26.27	26.42	30.96	29.82	29.87	29.70	30.21	30.35	30.07
C(7)	47.67	49.76	47.76	48.32	40.87	40.30	49.53	40.73	49.62	49.12	41.02	49.55	35.63
C(8)	20.40	19.99	20.36	20.10	29.57	29.47	21.15	26.55	20.39	21.36	26.66	21.47	28.04
C(9)	20.85	20.69	21.03	20.87	20.78	21.88	20.86	21.65	21.20	21.56	22.94	21.03	23.33
C(10)	10.10	11.82	10.46	11.73	17.79	17.80	10.63	17.17	11.12	11.08	17.79	11.19	17.12
C(11)	122.18	122.99	121.99	122.95	120.31	120.00	29.34	25.64	48.99	49.72	44.91	39.14	39.87
C(12)	–	–	0.96	1.11	–	1.07	118.61	119.41	–	–	–	39.27	44.53

[a] For the numbering of the bicyclic moiety see Scheme 1; the carbon atoms of the substituents were numbered continuously.

The following starting materials were used (commercially available or prepared according to the literature): (+)-camphor, (−)-fenchone, Me_3SiCN, $BF_3{\cdot}OEt_2$, $LiAlH_4$, *n*-BuLi (Fluka AG); $LiCH_2CN$;[11] anhydrous $CeCl_3$.[9]

3.2. (1*R*,2*R*)-2-Hydroxy-1,7,7-trimethylbicyclo-[2.2.1]hept-1-yl-carbonitrile 3, (1*R*,2*S*)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-1-yl-carbonitrile 4, (1*R*,2*R*)-2-trimethylsilyloxy-1,7,7-trimethyl-bicyclo-[2.2.1]hept-1-yl-carbonitrile 5 and (1*R*,2*S*)-2-trimethylsilyloxy-1,7,7-trimethylbicyclo[2.2.1]hept-1-yl-carbonitrile 6

To **1** (1.52 g, 9.98 mmol) were added $BF_3{\cdot}OEt_2$ (0.28 g, 1.97 mmol) and Me_3SiCN (1.19 g, 11.99 mmol) at rt. The mixture was stirred for 1 h at rt and for an additional 0.5 h at 60°C then diluted with Et_2O (70 mL). The reaction mixture was carefully hydrolyzed with 2N aq. HCl, washed with 5% aq. $NaHCO_3$, H_2O and dried (Na_2SO_4). After evaporation of the solvent, the crude product was chromatographed (∅ = 23 mm, *h* = 580 mm, 98 g silica gel, petroleum ether/Et_2O = 4:1) to give a mixture of **5**:**6** = 2:1 (by NMR) as a colorless oil (1.53 g, 61%) and a mixture of **3**:**4** = 2:1 (by NMR) as colorless crystals (0.65 g, 36%). The **3**/**4** mixture was chromatographed (∅ = 24 mm, *h* = 520 mm, 83 g silica gel, petroleum ether/Et_2O = 11:1) to give **3** (0.42 g, 23%), **4** (0.13 g, 7%) and a mixed fraction (0.01 g).

Data for **3**: Mp 159–160°C (in sealed capillary, otherwise sublimation occurs above 90°C). $[\alpha]_D^{20} = +7.4$ (*c* 0.85, $CHCl_3$). Anal. calcd for $C_{11}H_{17}NO$ (179.26): C, 73.70; H, 9.56; N, 7.81. Found: C, 73.50; H, 9.57; N, 7.99%. MS (EI) *m*/*z* (rel. int.): 179 ($M^{+\bullet}$, 1), 164 (3), 151 (4), 136 (4), 123 (5), 110 (25), 95 (100). ^1H NMR ($CDCl_3$, 300 K): $\delta = 2.48$ (s, 1H, OH), 2.24 (ddd, 1H, 3-H_{exo}, $J = 13.9$, 4.2, 1.3 Hz), 2.06 (d, 1H, 3-H_{endo}, $J = 13.9$ Hz), 1.86 (t, 1H, 4-H, $J = 4.2$ Hz), 1.58–1.84 (m, 3H, 5-H_{exo}, 6-H_{exo}, 6-H_{endo}), 1.20 (m, 1H, 5-H_{endo}), 1.04 (s, 3H, 8-H), 1.03 (s, 3H, 10-H), 0.89 (s, 3H, 9-H).

Data for **4**: Mp 181–182°C (in sealed capillary, otherwise sublimation occurs above 90°C). $[\alpha]_D^{20} = -20.8$ (*c* 0.87, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 K): $\delta = 2.42$ (s, 1H, OH), 2.62 (ddd, 1H, 3-H_{exo}, $J = 14.2$, 4.4, 1.2 Hz), 2.06 (m, 1H, 6-H_{endo}), 1.78 (dt, 1H, 4-H, $J = 4.4$, 2.0 Hz), 1.67–1.76 (m, 1H, 5-H_{exo}), 2.98 (d, 1H, 3-H_{endo}, $J = 14.2$ Hz), 1.18–1.43 (m, 2H, 5-H_{endo}, 6-H_{exo}), 1.10 (s, 3H, 8-H), 1.07 (s, 3H, 10-H), 0.93 (s, 3H, 9-H).

Data for **5**: MS (EI) *m*/*z* (rel. int.): 251 ($M^{+\bullet}$, 2), 236 (4), 209 (8), 110 (38), 95 (100). ^1H NMR ($CDCl_3$, 300 K): $\delta = 2.18$ (ddd, 1H, 3-H_{exo}, $J = 13.7$, 4.4, 1.7 Hz), 2.02 (d, 1H, 3-H_{endo}, $J = 13.7$ Hz), 1.48–1.81 (m, 4H, 4-H, 5-H_{endo}, 6-H_{exo}, 6-H_{endo}), 1.12–1.35 (m, 1H, 5-H_{exo}), 0.97 (s, 3H, 8-H), 0.93 (s, 3H, 10-H), 0.85 (s, 3H, 9-H), 0.21 (s, 9H, 12-H).

Data for **6**: ^1H NMR ($CDCl_3$, 300 K): $\delta = 2.56$ (ddd, 1H, 3-H_{exo}, $J = 13.8$, 4.4, 1.2 Hz), 2.02–2.14 (m, 1H, 6-H_{endo}) 1.48–1.81 (m, 2H, 4-H, 5-H_{exo}), 1.44 (d, 1H, 3-H_{endo}, $J = 13.8$ Hz), 1.12–1.35 (m, 2H, 5-H_{endo}, 6-H_{exo}), 1.08 (s, 3H, 8-H), 1.01 (s, 3H, 10-H), 0.90 (s, 3H, 9-H), 0.22 (s, 9H, 12-H).

3.3. (1*R*,2*R*)-2-Hydroxy-1,3,3-trimethylbicyclo-[2.2.1]hept-1-yl-carbonitrile 7 and (1*R*,2*R*)-2-hydroxy-1,3,3-trimethylsilyloxybicyclo[2.2.1]hept-1-yl-carbonitrile 8

To **2** (0.90 g, 5.91 mmol) were added $BF_3{\cdot}OEt_2$ (0.17 g, 1.20 mmol) and Me_3SiCN (0.71 g, 7.16 mmol) at rt. The mixture was stirred for 1 h at rt and for an additional 0.5 h at 60°C then diluted with Et_2O (50 mL). The mixture was carefully hydrolyzed with 2N aq. HCl, washed with 5% aq. $NaHCO_3$, H_2O and dried (Na_2SO_4). After evaporation of the solvent, the crude product was chromatographed (∅ = 24 mm, *h* = 520 mm, 86 g silica gel, petroleum ether/Et_2O = 5:1) to give **8** as a colorless oil (0.96 g, 64%) and **7** as colorless crystals (0.28 g, 26%).

Data for **7**: Mp 93°C. $[\alpha]_D^{20} = +17.1$ (*c* 0.87, $CHCl_3$). Anal. calcd for $C_{11}H_{17}NO$ (179.26): C, 73.70; H, 9.56; N, 7.81. Found: C, 73.65; H, 9.58; N, 7.93%. MS (EI) *m*/*z* (rel. int.): 179 ($M^{+\bullet}$, 10), 164 (28), 151 (25), 136 (35), 123 (28), 108 (25), 81 (75), 67 (100). ^1H NMR ($CDCl_3$, 300 K): $\delta = 2.36$ (s, 1H, OH), 1.83–1.92 (m, 1H, 6-H_{endo}), 1.80–1.85 (m, 1H, 4-H), 1.73–1.81 (m, 1H, 7-H_{syn}), 1.55–1.73 (m, 1H, 5-H_{endo}), 1.45 (dddd, 1H, 5-H_{exo}, $J = 12.5$, 9.8, 5.9, 3.9 Hz), 1.25–1.31 (m, 1H, 7-H_{anti}), 1.31 (s, 3H, 10-H), 1.25 (s, 3H, 8-H), 1.18 (dt, 1H, 6-H_{exo}, $J = 12.5$, 3.3 Hz), 0.98 (s, 3H, 9-H).

Data for **8**: $[\alpha]_D^{20} = +19.1$ (*c* 1.26, $CHCl_3$). MS (EI) *m*/*z* (rel. int.): 251 ($M^{+\bullet}$, 5), 236 (59), 223 (50), 208 (23), 168 (26), 141 (28), 123 (20), 109 (23), 81 (84), 69 (100). ^1H NMR ($CDCl_3$, 300 K): $\delta = 1.78$–1.89 (m, 1H, 6-H_{endo}), 1.74–1.78 (m, 1H, 4-H), 1.69–1.74 (m, 1H, 7-H_{syn}), 1.58–1.69 (m, 1H, 5-H_{endo}), 1.39 (dddd, 1H, 5-H_{exo}, $J = 12.2$, 10.0, 6.1, 3.9 Hz), 1.12–1.24 (m, 7-H_{anti}), 1.20 (s, 6H, 8-H, 10-H), 1.08 (td, 1H, 6-H_{exo}, $J = 12.5$, 3.2 Hz), 0.87 (s, 3H, 9-H), 0.23 (s, 9H, 12-H).

3.4. (1*R*,2*S*)-2-Cyanomethyl-2-hydroxy-1,7,7-trimethyl-bicyclo[2.2.1]heptane 9

A mixture of **1** (0.70 g, 4.60 mmol) and anhydrous $CeCl_3$ (1.13 g, 4.58 mmol) in THF (10 mL) was stirred for 1 h at rt. The mixture was cooled to −78°C, solid $LiCH_2CN{\cdot}THF$ (0.82 g, 6.89 mmol) was added rapidly at the same temperature and the mixture was allowed to warm to rt and stirred for a further 1.5 h. The mixture was treated with 2N aq. HCl, extracted with Et_2O (3×20 mL), washed with 5% aq. $NaHCO_3$, H_2O and dried (Na_2SO_4). After evaporation of the solvent, the crude product was chromatographed (∅ = 24 mm, *h* = 520 mm, 87 g silica gel, petroleum ether/Et_2O = 2:1) to afford **9** as a colorless solid (0.76 g, 85%). Mp 52–54°C. $[\alpha]_D^{20} = -3.6$ (*c* 2.00, $CHCl_3$). Anal. calcd for $C_{12}H_{19}NO$ (193.29): C, 74.57; H, 9.91; N, 7.25. Found: C, 75.59; H, 9.91; N, 7.38%. MS (EI) *m*/*z* (rel. int.): 193 ($M^{+\bullet}$, 8). ^1H NMR ($CDCl_3$, 300 K): $\delta = 2.57$ (s, 2H, 11-H), 2.15 (dt, 1H, 3-H_{exo}, $J = 15.0$, 2.5 Hz), 1.72–1.82 (m, 2H, 4-H, 5-H_{exo}), 1.46–1.62 (m, 2H, 3-H_{endo}, 6-

H_{exo}), 1.10 (s, 3H, 8-H), 0.92–1.10 (m, 2H, 5-H_{endo}, 6-H_{endo}), 0.97 (s, 3H, 10-H), 0.88 (s, 3H, 9-H).

3.5. (1*R*,2*R*)-2-Cyanomethyl-2-hydroxy-1,3,3-trimethylbicyclo[2.2.1]heptane 10

A mixture of **1** (0.70 g, 4.60 mmol) and anhydrous $CeCl_3$ (1.13 g, 4.58 mmol) in THF (10 mL) was stirred for 1 h at rt. The mixture was cooled to −78°C and solid $LiCH_2CN{\cdot}THF$ (0.82 g, 6.89 mmol) was added rapidly. The mixture was allowed to warm to rt and stirred for 1.5 h then treated with 2N aq. HCl, extracted with Et_2O (3×20 mL), washed with 5% aq. $NaHCO_3$, H_2O and dried (Na_2SO_4). After evaporation of the solvent, the crude product was chromatographed (∅ = 24 mm, *h* = 520 mm, 87 g silica gel, petroleum ether/Et_2O = 2:1) to afford **9** as a colorless solid (0.72 g, 81%). Mp 95–96°C. $[\alpha]_D^{20} = -17.1$ (*c* 2.00, $CHCl_3$). Anal. calcd for $C_{12}H_{19}NO$ (193.29): C, 74.57; H, 9.91; N, 7.25. Found: C, 75.11; H, 10.03; N, 7.25%. MS (EI) *m*/*z* (rel. int.): 193 ($M^{+\bullet}$, 7). ^1H NMR ($CDCl_3$, 300 K): $\delta = 2.44$ (s, 2H, 11-H), 2.08 (s, 1H, OH), 1.84–1.95 (m, 1H, 6-H_{endo}), 1.59–1.69 (m, 2H, 4-H, 5-H_{endo}), 1.49 (dq, 1H, 7-H_{syn}, $J = 10.4$, 2.2), 1.33–1.34 (m, 1H, 5-H_{exo}), 1.10 (s, 3H, 8-H), 1.00–1.18 (m, 2H, 6-H_{exo}, 7-H_{anti}), 1.00 (s, 3H, 10-H), 0.97 (s, 3H, 9-H).

3.6. (1*R*,2*R*)-2-Aminomethyl-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane 11

A suspension of $LiAlH_4$ (0.20 g, 5.27 mmol) in Et_2O (20 mL) was treated with a solution of **3** (0.14 g, 0.78 mmol) in Et_2O (10 mL) dropwise at rt and the mixture was stirred for 4 h at rt. Aqueous 2N HCl was added and the mixture was washed (3×10 mL Et_2O) and rendered alkaline by addition of aq. NaOH. The alkaline phase was extracted with Et_2O (3×10 mL) and the extract was dried (Na_2SO_4). Evaporation of the solvent afforded of **11** as colorless crystals (0.091 g, 65%). Mp 44–47°C. $[\alpha]_D^{20} = -5.5$ (*c* 1.00, $CHCl_3$). Anal. calcd for $C_{11}H_{21}NO$ (183.29): C, 72.08; H, 11.55; N, 7.64. Found: C, 71.97; H, 11.63; N, 7.71%. MS (EI) *m*/*z* (rel. int.): 183 ($M^{+\bullet}$, 5), 165 (5), 153 (75), 108 (83), 95 (100). ^1H NMR ($CDCl_3$, 300 K): $\delta = 2.76$ (d, 1H, 11-H_a, $J = 12.2$ Hz), 2.67 (d, 1H, 11-H_b, $J = 12.2$ Hz), 1.94 (dt, 1H, 3-H_{exo}, $J = 13.0$, 3.8 Hz), 1.69 (t, 1H, 4-H, $J = 2.7$ Hz), 1.62–1.76 (m, 1H, 5-H_{exo}), 1.21–1.45 (m, 2H, 6-H_{exo}, 6-H_{endo}), 1.23 (d, 1H, 3-H_{endo}, $J = 13.0$ Hz), 0.87–1.11 (m, 1H, 5-H_{endo}), 1.11 (s, 3H, 8-H), 0.86 (s, 3H, 10-H), 0.83 (s, 3H, 9-H).

3.7. (1*R*,2*S*)-2-Aminomethyl-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane 12

A suspension of $LiAlH_4$ (0.20 g, 5.27 mmol) in Et_2O (20 mL) was treated with a solution of **4** (0.08 g, 0.45 mmol) in Et_2O (10 mL) dropwise at rt and the mixture was stirred for 4 h at rt. The mixture was carefully hydrolyzed with 2N aq. HCl, the acidic layer was washed (3×10 mL Et_2O) and rendered alkaline by addition of aq. NaOH. The alkaline phase was extracted with Et_2O (3×10 mL) and the extract was dried (Na_2SO_4). Evaporation of the solvent afforded **12** as colorless crystals (0.08 g, 98%). Mp 55–56°C. $[\alpha]_D^{20} = -20.0$ (*c* 1.00, $CHCl_3$). Anal. calcd for $C_{11}H_{21}NO$ (183.29): C, 72.08; H, 11.55; N, 7.64. Found: C, 72.00; H, 11.62; N, 7.71%. MS (EI) *m*/*z* (rel. int.): 183 ($M^{+\bullet}$, 5), 165 (7), 153 (48), 108 (70), 95 (100). ^1H NMR ($CDCl_3$, 300 K): $\delta = 2.82$ (d, 1H, 11-H_a, $J = 12.8$ Hz), 2.65 (d, 1H, 11-H_b, $J = 12.8$ Hz), 2.18 (m, 1H, 6-H_{endo}), 1.90 (dt, 1H, 3-H_{exo}, $J = 13.3$, 3.7 Hz), 1.63–1.77 (m, 1H, 5-H_{exo}), 1.64 (m, 1H, 4-H), 1.15–1.34 (m, 2H, 5-H_{endo}, 6-H_{exo}), 1.20 (d, 1H, 3-H_{endo}, $J = 13.3$ Hz), 0.88 (s, 3H, 8-H), 0.87 (s, 3H, 9-H), 0.75 (s, 3H, 10-H).

3.8. (1*R*,2*R*)-2-Aminomethyl-2-hydroxy-1,3,3-trimethylbicyclo[2.2.1]heptane 13

A suspension of $LiAlH_4$ (0.18 g, 4.73 mmol) in Et_2O (20 mL) was treated with a solution of **7** (0.10 g, 0.56 mmol) in Et_2O (10 mL) dropwise at rt and stirred for 4 h at rt. The mixture was carefully hydrolyzed with 2N HCl, and washed (3×10 mL Et_2O) then rendered alkaline by addition of aq. NaOH. The alkaline phase was extracted with Et_2O (3×10 mL) and the extract was dried (Na_2SO_4). Evaporation of the solvent afforded **13** as colorless crystals (0.03 g, 29%). Mp 59–61°C. $[\alpha]_D^{20} = -12.5$ (*c* 1.24, $CHCl_3$). Anal. calcd for $C_{11}H_{21}NO$ (183.29): C, 72.08; H, 11.55; N, 7.64. Found: C, 71.99; H, 11.60; N, 7.69%. MS (EI) *m*/*z* (rel. int.): 183 ($M^{+\bullet}$, 4), 168 (12), 153 (34), 109 (16), 100 (28), 97 (18). 81 (100). ^1H NMR ($CDCl_3$, 300 K): $\delta = 2.82$ (d, 1H, 11-H_a, $J = 13.0$ Hz), 2.71 (d, 1H, 11-H_b, $J = 13.0$ Hz), 2.10 (dddd, 1H, 6-H_{endo}, $J = 12.2$, 9.2, 5.1, 2.4 Hz), 1.74 (m, 1H, 5-H_{endo}), 1.54 (dq, 1H, 7-H_{syn}, $J = 10.0$, 2.4, 2.2, 1.7 Hz), 1.51–1.58 (m, 1H, 4-H), 1.38 (dddd, 1H, 5-H_{exo}, $J = 12.5$, 12.1, 5.1, 4.2 Hz), 1.06 (dd, 1H, 7-H_{anti}, $J = 10.0$, 1.5 Hz), 0.87–0.99 (td, 1H, 6-H_{exo}, $J = 12.5$, 4.2 Hz), 0.96 (s, 6H, 8-H, 10-H), 0.94 (s, 3H, 9-H).

3.9. (1*R*,2*S*)-2-(2-Aminoethyl)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane 14

A suspension of $LiAlH_4$ (0.12 g, 3.16 mmol) in Et_2O (30 mL) was treated with a solution of **9** (0.51 g, 2.64 mmol) in Et_2O (10 mL) dropwise at rt and stirred for 2 h at rt. The mixture was carefully hydrolyzed with 2N HCl, the acidic layer was washed (3×10 mL Et_2O) and rendered alkaline by addition of aq. Na_2CO_3. The alkaline phase was extracted with Et_2O (3×30 mL) and the extract was dried (Na_2SO_4). Evaporation of the solvent afforded **14** as a waxy solid (0.47 g, 90%). $[\alpha]_D^{20} = -11.8$ (*c* 3.00, $CHCl_3$). MS (CI-NH_3) *m*/*z* (rel. int.): 198 ($[M+H]^+$, 100), 180 ($[(M-H_2O)+H]^+$, 19). ^1H NMR ($CDCl_3$, 300 K): $\delta = 4.70$ (s, 1H, OH), 2.94–3.15 (m, 2H, 12-H), 2.05 (dt, 1H, 3-H_{exo}, $J = 12.9$, 3.9 Hz), 1.50–1.75 (m, 4H, 4-H, 5-H_{exo}, 11-H), 1.30–1.42 (m, 3H, 3-H_{endo}, 6-H), 0.82–1.01 (m, 1H, 5-H_{endo}), 1.08 (s, 3H, 8-H), 0.90 (s, 3H, 10-H), 0.84 (s, 3H, 9-H).

3.10. (1*R*,2*R*)-2-(2-Aminoethyl)-2-hydroxy-1,3,3-trimethylbicyclo[2.2.1]heptane 15

A suspension of $LiAlH_4$ (0.12 g (3.16 mmol) in Et_2O (30 mL) was treated with a solution of **9** (0.51 g, 2.64 mmol) in Et_2O (10 mL) dropwise at rt and stirred for 2

h at rt. The mixture was carefully hydrolyzed with 2N HCl, the acidic layer was washed (3×10 mL Et_2O) and rendered alkaline by addition of aq. Na_2CO_3. The alkaline phase was extracted with Et_2O (3×30 mL) and the extract was dried (Na_2SO_4). Evaporation of the solvent afforded **14** as a colorless solid (0.50 g, 96%). Mp 74–76°C (decomp.). $[\alpha]_D^{20}=-30.4$ (*c* 1.50, $CHCl_3$). Anal. calcd for $C_{12}H_{23}NO$ (197.32): C, 73.04; H, 11.75; N, 7.10. Found: C, 72.95; H, 11.64; N, 7.25%. MS (CI-NH_3) *m*/*z* (rel. int.): 198 ($[M+H]^+$, 100), 180 ($[(M-H_2O)+H]^+$, 24). ^1H NMR ($CDCl_3$, 300 K): $\delta=2.92$–3.13 (m, 2H, 12-H), 2.22 (s, 1H, OH), 2.02–2.14 (m, 1H, 6-H_{endo}), 1.67–1.77 (m, 2H, 11-H), 1.48–1.63 (m, 3H, 4-H, 5-H_{endo}, 7-H_{syn}), 1.30–1.44 (m, 1H, 5-H_{exo}), 0.86–1.08 (m, 2H, 6-H_{exo}, 7-H_{anti}), 1.03 (s, 3H, 8-H), 1.02 (s, 3H, 10-H), 1.01 (s, 3H, 9-H).

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