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Synthesis of new enantiopure aminodiols and their use as ligands for the addition of diethylzinc to benzaldehyde

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Abstract

The synthesis of new enantiopure aminodiols through aminolytic ring opening of chiral epoxy alcohols derived from (+)-camphor and (−)-fenchone is described. The absolute configurations were determined by NMR methods. The aminodiols catalyzed the addition of diethylzinc to benzaldehyde in high yields and with enantioselectivities of up to 80%.

1. Introduction

The enantioselective addition of dialkylzinc compounds to aldehydes catalyzed by chiral amino-alcohols has been intensively investigated because the preparation of enantiomerically pure or enriched alcohols is important, particularly since they are often valuable intermediates for the synthesis of natural products.[1] Therefore, it is not surprising that the preparation of new chiral aminoalcohols for such addition reactions has been an object of increased interest. In general, mainly β-aminoalcohols have been applied as catalysts, since Noyori demonstrated the high activity of (−)-3-*exo*-dimethylamino isoborneol.[2] However, a few examples of the use of γ-[3] and δ-aminoalcohols,[4] also derived from camphor and fenchone,[5,6] have recently demonstrated their utility as catalysts for asymmetric addition of dialkylzincs to aldehydes. In this connection, the syntheses of compounds based on strategies using (+)-camphor and (−)-fenchone are of increased importance and we have recently reported other results, including the synthesis of chiral aminoalcohols,[5] and the preparation of new chiral epoxyalcohols incorporating their skeletons.[7] These epoxyalcohols are suitable sources for aminolytic ring opening which results in the formation of chiral aminodiols. In this paper we present investigations concerning their preparation and application as ligands. To date, there are only a few examples of the use of aminodiols as catalysts in addition reactions of dialkylzincs to aldehydes.[8]

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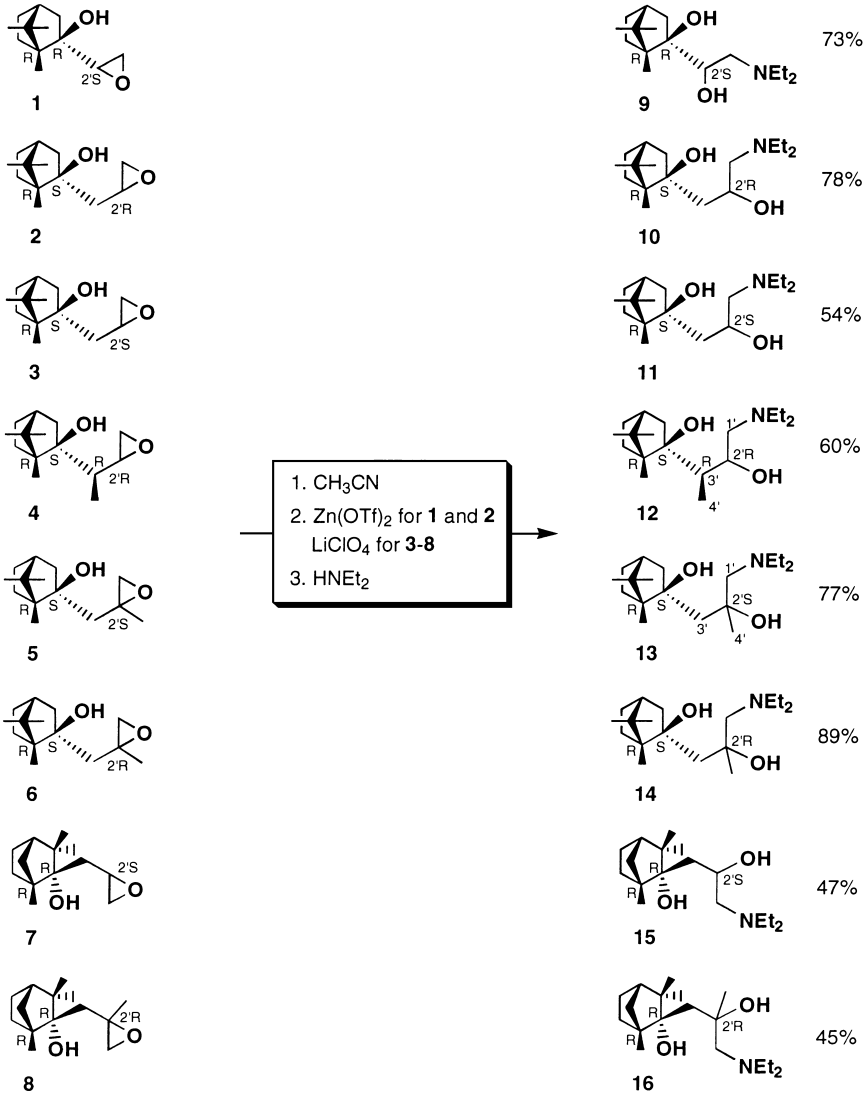
2. Results and discussion

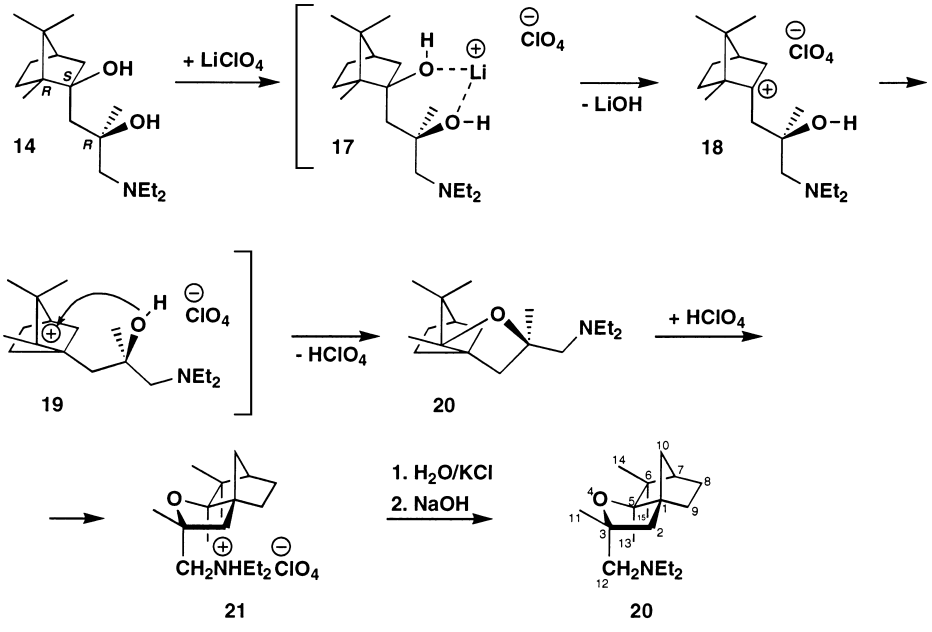
The aminolytic cleavage of the epoxyalcohols **1**–**8**, prepared by previously published procedures, was carried out using acetonitrile as a solvent with an excess of Et_2NH (Scheme 1). The reactions were relatively slow at room temperature; therefore, for the syntheses of products **9**, **12**, **13** and **16** it was necessary to warm the mixtures to 50°C. The assistance of metal salts was obligatory in all cases: $Zn(OTf)_2$ for the aminolysis of **1** and **2**, and $LiClO_4$ for compounds **3**–**8**. Aminodiols **9**–**16** were isolated in pure form and good yields after acidic workup of the reaction mixtures followed by treatment of the acidic aqueous layers with 2 N NaOH and extraction after that with Et_2O.



Scheme 1.

The aminolytic cleavage proceeded in all cases with excellent regioselectivities at the less substituted carbon atom of the epoxide and therefore with retention of the configuration. These observations are in agreement with previously published data.[9]

In the case of homoallyl alcohol **6**, an attempt to carry out the aminolysis more quickly (the reaction of **6** to **14** at room temperature proceeds within 4 days with 89% yield), by raising the temperature to 50°C, resulted in a quantitative conversion within 10 h of **14** to a new product, recognized as the oxatricyclic diethylamino perchlorate derivative **21**. For the formation of **21** we suggest the interpretation presented in Scheme 2, in which the decisive step includes the formation of carbonium ion **18**, most probably with the participation of $LiClO_4$ (coordination of the Li ion to the oxygen moieties, structure **17**). Rearrangement to **19** followed by ring closure to compound **20**, led, under the reaction conditions, to the isolation of product **21**. Treatment of an aqueous solution of **21** with KCl, and then with NaOH, quantitatively produced the diethylamino oxatricyclic compound **20**. The described kind of carbonium ion generation followed by rearrangement has been observed in previous investigations[7a] and has also been reported recently in other literature.[10] Products **20** and **21** have similar NMR data compared with a structurally identical oxatricyclic derivative previously prepared.[7a] The observed coupling constants between 12-H and N–H protons for compound **21**, disappearing after D_2O exchange, confirm its ammonium salt structure.

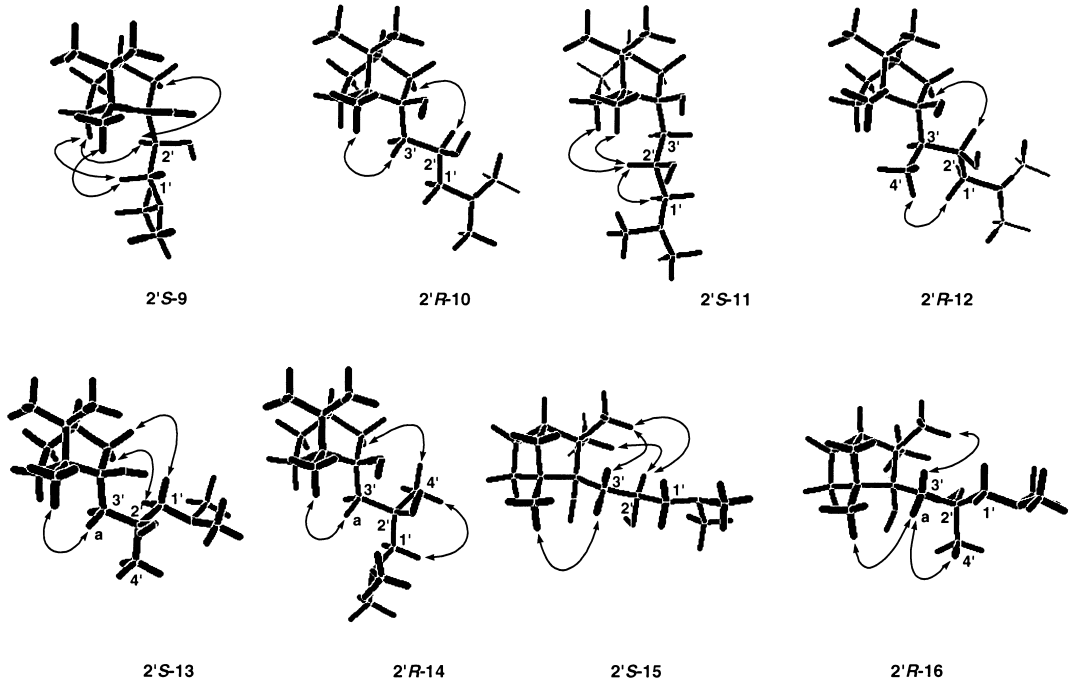


Scheme 2.

The absolute configurations of the aminoalcohols could be deduced in principle from that of the starting compounds **1**–**8**, since the aminolytic cleavage of the epoxides proceeds with retention of the configuration at the 2′-carbon atom. Nevertheless, we decided to unambiguously determine the configurations of **9**–**16** in order to reconfirm our previous investigations.[7] We used the same approach, i.e. reducing the relative configuration and conformation in the side chain using coupling constant information, NOE distance constraints and force field calculations, corroborated by chemical shift arguments. The distinct considerations are listed below.

For **9**: the NMR data reveal the orientation of the side chain of **9** as depicted in Scheme 3. The smallest substituent 2′-H points to the *endo*-side of the bicyclic skeleton (NOEs with 3-H_{endo}, 6-H_{endo}). The 1′-H_{gauche} is on the side of the 10-H methyl protons, in line with 2′*S*-configuration.

Compounds **10** and **11**, diastereoisomers obtained by the aminolysis of the individual diastereoisomers **2** and **3**, possess very close spectral data (chemical shifts and coupling constants). In both compounds



Scheme 3.

the side chains show antiperiplanar conformation, as revealed by the measured vicinal coupling constants and the observed NOEs only between 1′ and 3′ *anti*- and between 1′ and 3′ *gauche*-protons, respectively. Similarly, as in the starting epoxyalcohols **2** and **3**, the 3′-H_{anti} proton for **10** is situated near the 10-H methyl protons, whereas this is the case for the 3′-H_{gauche} in **11**. Additionally, the 2′-H proton in **10** is near the 3-H_{endo} and in the case of **11** on the side of 10-H methyl protons. The data are in accordance only with 2′*R*-configuration for **10** and 2′*S* for **11** in the conformations depicted in Scheme 3.[‡]

For **12**: the NOEs observed between the 2′-H proton and the 3-H_{endo}, 1′-H_{gauche} and 3′-H protons are possible only in the case of 2′*R*-configuration. In addition, the measured vicinal coupling constants and the NOE between 1′-H_{anti} and 4′-H methyl protons are in accordance with the calculated predominant conformer.

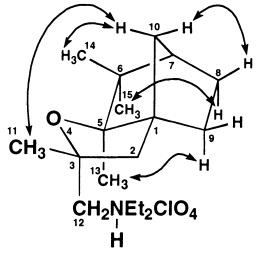
The diastereoisomers **13** and **14** are prepared by aminolysis of the individual **5** and **6**, respectively. The proton labelled as 3′-H_a is near the 10-H methyl protons in both diastereoisomers. In **13** the 4′-methyl group is close to the 3′-H_a, whereas the 1′-CH_2 protons show NOEs with C-3 protons of the bicyclic skeleton indicating 2′*S*-configuration. Conversely, in **14** according to the 2′*R*-configuration, the 4′-methyl protons are near the 3-H_{endo} proton. The observed shielding for C-1′ in **13** with 5 ppm and with 2 ppm for C-4′ in **14**, due to the γ-*gauche* interaction with the C-2 atom of the skeleton, respectively, corroborates the assignment made.

For **15**: the 2′-H proton is near the 8-H, 9-H protons of the geminal methyl groups, whereas 3′-H_{anti} is near the 10-H methyl protons, confirming 2′*S*-configuration.

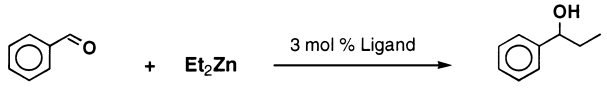
For **16**: the 4′-methyl protons are in close proximity to the 3′-H_a proton, which is situated near the 10-H methyl protons. These observations are compatible with 2′*R*-configuration.

[‡] It must be pointed out here that in the previous report[7a] the assignments for the configurations of the 2′-carbon atom in **2** and **3** were changed as a result of a confusing mistake.

For **21**: the structure and absolute configuration of the oxatricyclic derivative **21** were unambiguously determined from its NMR data. The observed NOEs are illustrated below.



The aminodiols **9**–**16** were tested in pure form as catalysts (3 mol%) for the addition of Et_2Zn to benzaldehyde, as well as, in some cases, in the form of in situ formed Li–alkoxide species prepared after treatment with one or two equivalents of *n*-BuLi (Table 1). In most cases, the yields of the isolated 1-phenyl-1-propanol were high, however the reactions were relatively slow, with the exception of the reaction catalyzed by ligand **9** (Table 1, entries 1 and 2). The best enantioselectivities were obtained with the aminodiols **9** and **13** (entries 1 and 9). The enantioselectivities with ligands **10**, **12** and **14**–**16** were low and in the case of aminodiol **11** no asymmetric induction was observed. The use of *n*-BuLi for in situ formation of Li salts of the aminodiols was in accordance with recently published investigations in which the Li–alkoxides of some chiral diethanolamines showed a better reactivity and selectivity compared with the pure aminodiols.[8b] However, in our experiments treatment of compounds **9** and **13** with *n*-BuLi led to a significant decrease of the enantioselectivity (entries 2 and 10). In all other cases the changes of the enantioselectivity observed after addition of *n*-BuLi were unimportant (Table 1). The results obtained allow us to assume that ligands from the investigated structural type having a shorter side chain, as in the case of **9**, would lead to better enantioselectivities.



Ligand: Aminodiol
Aminodiol + 1 eq. n-BuLi
Aminodiol + 2 eq. n-BuLi

In conclusion, we have effectively prepared new chiral aminodiols. Determination of the absolute configuration confirmed the utility of the NMR approach used. The aminodiols have been successfully applied as catalysts for enantioselective addition of diethylzinc to benzaldehyde.

3. Experimental

3.1. General methods

All reactions with diethylzinc were carried out in flame-dried Schlenk flasks under argon atmosphere. The solvents for these reactions, hexane and toluene, were dried with $Na[Et_4Al]$ and distilled. Thin layer chromatography (TLC): aluminium sheets precoated with silica gel 60 F_{254} (Merck). Column chromatography: at normal pressure, silica gel 60 (0.040–0.063 nm, Merck). $[\alpha]_D^{20}$: Perkin–Elmer 241 polarimeter. Mass spectra (MS): Finnigan MAT 90 or Finnigan SSQ 700; fragmentation in *m/z* with relative intensities (%) in parentheses. NMR spectra: Bruker AVANCE DRX-250 (^{1}H at 250.1 MHz; ^{13}C at 62.9 MHz; TMS as internal standard). Elemental analyses were performed by the Microanalytical Service Laboratory of the Institute of Organic Chemistry, Bulgarian Academy of Sciences.

Table 1
Addition of diethylzinc to benzaldehyde catalyzed by aminodiols **9**–**16**

Entry	Catalyst	Solvent[a]	Equivalent n-BuLi	Reaction Time [h]	Yield[b] [%]	Optical Purity[c] [%]
1	**9**	hexane/toluene	-	24	93	80 (S)
2	**9**	hexane	2	24	93	55 (S)
3	**10**	toluene	-	48	33	26 (R)
4	**10**	hexane/toluene	2	60	51	21 (R)
5	**11**	hexane/toluene	-	100	92	0
6	**12**	toluene	-	94	44	26 (R)
7	**12**	toluene	2	74	62	37 (R)
8	**12**	hexane/toluene	1	100	75	34 (R)
9	**13**	hexane/toluene	-	72	76	73 (R)
10	**13**	hexane/toluene	2	72	71	50 (R)
11	**14**	hexane/toluene	-	72	79	35 (S)
12	**15**	hexane/toluene	-	96	45	12 (S)
13	**15**	hexane/toluene	2	100	58	18 (S)
14	**16**	hexane/toluene	-	72	83	8 (R)

[a]The ratio hexane/toluene was 2/1 (v/v). [b]Yields of isolated 1-phenyl-1-propanol (after Kugelrohr distillation or column chromatography). [c]Determined by polarimetry based on the maximum values described for the specific rotations of *S*-(-)- and *R*-(+)-1-phenyl-1-propanol.[4,5]

3.2. Starting materials

The following starting materials (commercially available or prepared according to the literature) were used: epoxyalcohols **1**–**8**,[11] lithium perchlorate ($LiClO_4$; Fluka AG), zinc trifluoromethanesulfonate ($Zn(OTf)_2$; Fluka AG), diethylzinc solution (1 M in hexane or 1.1 M in toluene; Fluka AG) (Table 2).

*3.3. General procedure for the aminolysis of epoxyalcohols **1**–**8** in the presence of metal salts*

A solution of the corresponding epoxyalcohol **1**–**8** (0.45–1.00 mmol) in acetonitrile was treated with an equimolar quantity of the corresponding metal salt ($Zn(OTf)_2$ or $LiClO_4$) and then stirred until complete dissolution of the salt was obtained. To this solution a fivefold excess of Et_2NH was introduced and the mixture was stirred until completion of the reaction (monitored by TLC). The duration and temperature for each individual reaction are given below. After completion of the reaction the mixture was treated with 2 N HCl and unreacted epoxyalcohol was extracted with Et_2O. The acidic aqueous layer was made alkaline with 2 N NaOH and extracted with Et_2O. Evaporation of the washed (H_2O) and dried (Na_2SO_4) ether extract yielded the corresponding aminodiol (pure by NMR and elemental analysis).

*3.4. (1*R,*2*R,*2′*S*)-2*-endo-*(1′-Diethylamino-2′-hydroxyethyl)-1,7,7-trimethylbicyclo[2.2.1]heptane-2-ol **9***

Following the general procedure, 0.10 g (0.51 mmol) of **1** in 4 ml CH_3CN, 0.18 g (0.51 mmol) $Zn(OTf)_2$ and 0.18 g (2.25 mmol) Et_2NH were combined and stirred for 30 h at 50°C to give 0.10 g

Table 2
^{13}C NMR chemical shifts for compounds **9**–**16** and **20**, **21** in $CDCl_3$

C-atom No.*	9	10	11	12	13	14	15	16	20	21
1	50.40	52.30	51.98	52.35	53.48	53.23	52.61	53.23	59.29	58.32
2	79.72	80.99	80.66	83.89	79.82	79.51	80.99	80.66	40.23	40.80
3	47.13	46.35	48.31	48.60	50.23	49.12	44.45	46.16	84.34	80.65
4	44.62	45.11	44.68	44.52	45.74	45.55	50.59	49.31	-	-
5	27.42	26.85	26.00	27.74	26.90	26.89	25.00	25.74	91.63	94.13
6	29.41	30.28	30.38	29.71	29.52	29.77	30.05	29.36	45.85	46.07
7	50.23	48.96	49.82	50.55	48.28	48.16	40.86	41.64	50.08	49.75
8	21.16	21.43	21.22	21.46	21.45	21.39	28.27	29.26	22.87	22.52
9	20.20	20.88	20.88	20.94	20.88	20.90	23.04	22.39	27.26	26.81
10	11.84	10.33	11.70	12.53	9.99	10.41	17.86	19.53	39.91	39.61
1′	53.87	59.93	60.16	57.37	61.79	66.95	59.86	67.27	27.26 (C-11)	25.75
2′	72.71	65.12	65.29	68.36	73.27	73.06	66.17	73.31	64.99 (C-12)	63.00
3′	-	41.58	44.68	44.02	46.75	46.74	39,68	41.31	20.56 (C-13)	20.33
4′	-	-	-	9.33	30.32	28.11	-	29.47	25.18 (C-14)	24.90
N-CH_2	47.03	46.78	47.07	47.16	48.41	48.16	47.06	47.81	22.61 (C-15)	22.48
N-C-CH_3	12.06	11.82	11.60	12.05	11.47	11.10	12.00	10.30	47.84 (N-CH_2)	47.39
									10.94 (N-C-CH_3)	8.82 7.53

*assignments are based on heteronuclear CH-correlation experiments (HSQC)[12]; for the numbering of the C-atoms see Schemes 1 and 2.

(73%) of **9**. Anal. calcd for $C_{16}H_{31}NO_2$ (269.4): C, 71.33; H, 11.60; N, 5.2; found: C, 71.78; H, 11.43; N, 5.10. $[\alpha]_D^{20}$: −47.6 (*c*=0.93, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 K): δ=0.82 (s, 3H, 9-H), 0.87 (s, 3H, 10-H), 1.03–1.12 (m, 1H, 5-H_{endo}), 1.03 (t, 6H, N–C–CH_3, *J*=7.1 Hz), 1.12 (s, 3H, 8-H), 1.19–1.29 (m, 1H, 6-H_{endo}), 1.34–1.46 (m, 1H, 6-H_{exo}), 1.66–1.80 (m, 2H, 5-H_{exo}, 4-H), 1.72 (d, 1H, 3-H_{endo}, *J*=13.2 Hz), 2.00 (dt, 1H, 3-H_{exo}, *J*=13.2, 3.9 Hz), 2.46 (dd, 1H, 1′-H_{gauche}, *J*=12.7, 3.9 Hz), 2.49 (dq, 2H, N–CH_2, *J*=13.8, 7.1 Hz), 2.63 (dd, 1H, 1′-H_{anti}, *J*=12.7, 10.5 Hz), 2.65 (dq, 2H, N–CH_2, *J*=13.7, 7.1 Hz), 3.53 (dd, 1H, 2′-H, *J*=10.5, 3.9 Hz).

*3.5. (1*R,*2*S,*2′*R*)-2*-endo-*(1′-Diethylamino-2′-hydroxypropyl)-1,7,7-trimethylbicyclo[2.2.1]heptane-2-ol* ***10***

Following the general procedure, 0.10 g (0.48 mmol) of **2** in 4 ml CH_3CN, 0.17 g (0.48 mmol) $Zn(OTf)_2$ and 0.17 g (2.38 mmol) Et_2NH were combined and stirred for 48 h at room temperature to give 0.10 g (78%) of **10**. MS (CI: NH_3) *m/z* (%): 284 ($[M+1]^+$, 100). Anal. calcd for $C_{17}H_{33}NO_2$ (283.4): C, 72.05; H, 11.74; N, 4.94; found: C, 72.46; H, 11.45; N, 4.84. $[\alpha]_D^{20}$: +35.4 (*c*=1.15, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 K): δ=0.84 (s, 3H, 9-H), 0.84–0.98 (m, 1H, 5-H_{endo}), 0.86 (s, 3H, 10-H), 1.00 (t, 6H, N–C–CH_3, *J*=7.1 Hz), 1.13 (s, 3H, 8-H), 1.24–1.43 (m, 2H, 6-H), 1.37 (d, 1H, 3-H_{endo}, *J*=13.0 Hz), 1.40 (dd, 1H, 3′-H_{gauche}, *J*=14.0, 2.0 Hz), 1.55–1.70 (m, 2H, 5-H_{exo}, 4-H), 1.56 (dd, 1H, 3′-H_{anti}, *J*=14.0, 9.3 Hz), 2.10 (dt, 1H, 3-H_{exo}, *J*=13.0, 3.9 Hz), 2.28 (dd, 1H, 1′-H_{anti}, *J*=12.7, 9.8 Hz), 2.38 (dd, 1H,

1′-H$_{gauche}$, *J*=12.7, 3.9 Hz), 2.49 (dq, 2H, N–CH$_2$, *J*=13.7, 7.1 Hz), 2.63 (dq, 2H, N–CH$_2$, *J*=13.7, 7.1 Hz), 3.9 (tdd, 1H, 2′-H, *J*=9.8, 3.9, 2.0 Hz), 4.19 (s, br, OH).

*3.6. (1*R,*2*S,*2′*S*)-2*-endo-*(1′-Diethylamino-2′-hydroxypropyl)-1,7,7-trimethylbicyclo[2.2.1]heptane-2-ol* **11**

Following the general procedure, 0.120 g (0.57 mmol) of **3** in 5 ml CH$_3$CN, 0.061 g (0.57 mmol) LiClO$_4$ and 0.210 g (2.80 mmol) Et$_2$NH were combined and stirred for 72 h at room temperature to give 0.090 g (56%) of **11**. $[\alpha]_D^{20}$: +34.2 (*c*=1.24, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 300 K): δ=0.80 (s, 3H, 9-H), 0.86–1.04 (m, 1H, 5-H$_{endo}$), 0.94 (s, 3H, 10-H), 0.99 (t, 6H, N–C–CH$_3$, *J*=7.1 Hz), 1.06 (s, 3H, 8-H), 1.16–1.27 (m, 1H, 6-H$_{endo}$), 1.29 (d, 1H, 3-H$_{endo}$, *J*=13.0 Hz) 1.29–1.47 (m, 1H, 6-H$_{exo}$), 1.55 (dd, 1H, 3′-H$_{anti}$, *J*=14.7, 9.5 Hz), 1.61 (m, 1H, 4-H), 1.63–1.75 (m, 1H, 5-H$_{exo}$), 1.66 (dd, 1H, 3′-H$_{gauche}$, *J*=14.7, 3.2 Hz), 2.00 (dt, 1H, 3-H$_{exo}$, *J*=13.2, 4.2 Hz), 2.22 (dd, 1H, 1′-H$_{anti}$, *J*=12.7, 9.5 Hz), 2.39 (dd, 2H, 1′-H$_{gauche}$, *J*=12.7, 3.9 Hz), 2.47 (dq, 2H, N–CH$_2$, *J*=13.3, 7.1 Hz), 2.60 (dq, 2H, N–CH$_2$, *J*=13.3, 7.1 Hz), 3.91 (tt, 1H, 2′-H, *J*=9.5, 3.7 Hz).

*3.7. (1*R,*2*S,*2′*R,*3′*R*)-2*-endo-*(1′-Diethylamino-2′-hydroxy-3′-methylpropyl)-1,7,7-trimethylbicyclo-[2.2.1]heptane-2-ol* **12**

Following the general procedure, 0.200 g (0.9 mmol) of **4** in 6 ml CH$_3$CN, 0.096 g (0.9 mmol) LiClO$_4$ and 0.330 g (4.5 mmol) Et$_2$NH were combined and stirred for 30 h at 50°C to give 0.158 g (60%) of **12**. MS (CI: NH$_3$) *m/z* (%): 298 ([M+1]$^+$, 100). Anal. calcd for C$_{18}$H$_{35}$NO$_2$ (297.5): C, 72.67; H, 11.86; N, 4.71; found: C, 72.14; H, 11.46; N, 4.79. $[\alpha]_D^{20}$: −21.6 (*c*=1.05, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 300 K): δ=0.82 (s, 3H, 9-H), 0.85–1.05 (m, 1H, 5-H$_{endo}$), 0.98 (s, 3H, 10-H), 0.98 (d, 3H, 4′-H, *J*=6.9 Hz), 1.02 (t, 6H, N–C–CH$_3$, *J*=7.1 Hz), 1.11 (s, 3H, 8-H), 1.34–1.51 (m, 2H, 6-H), 1.36 (d, 1H, 3-H$_{endo}$, *J*=13.0 Hz), 1.45 (q, 1H, 3′-H, *J*=6.9 Hz), 1.65–1.78 (m, 2H, 5-H$_{exo}$, 4-H), 2.17 (dt, 1H, 3-H$_{exo}$, *J*=13.0, 4.1 Hz), 2.23 (dd, 1H, 1′-H$_{gauche}$, *J*=12.7, 4.2 Hz), 2.46 (dd, 1H, 1′-H$_{anti}$, *J*=12.7, 10.3 Hz), 2.52 (dq, 2H, N–CH$_2$, *J*=13.4, 7.1 Hz), 2.64 (dq, 2H, N–CH$_2$, *J*=13.4, 7.1 Hz), 3.76 (s, br, OH), 4.06 (dd, 1H, 2′-H, *J*=10.3, 4.2 Hz).

*3.8. (1*R,*2*S,*2′*S*)-2*-endo-*(1′-Diethylamino-2′-hydroxy-2′-methylpropyl)-1,7,7-trimethylbicyclo[2.2.1]-heptane-2-ol* **13**

Following the general procedure, 0.100 g (0.45 mmol) of **5** in 4 ml CH$_3$CN, 0.048 g (0.45 mmol) LiClO$_4$ and 0.160 g (2.25 mmol) Et$_2$NH were combined and stirred for 25 h at 50°C to give 0.100 g (77%) of **13**. Anal. calcd for C$_{18}$H$_{35}$NO$_2$ (297.5): C, 72.67; H, 11.86; N, 4.71; found: C, 72.59; H, 11.59; N, 4.67. $[\alpha]_D^{20}$: +3.2 (*c*=1.07, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 300 K): δ=0.84 (s, 3H, 9-H), 0.84–1.05 (m, 1H, 5-H$_{endo}$), 0.87 (s, 3H, 10-H), 1.03 (t, 6H, N–C–CH$_3$, *J*=7.1 Hz), 1.11 (s, 3H, 8-H), 1.17 (s, 3H, 4′-H), 1.23–1.45 (m, 2H, 6-H), 1.45 (d, 1H, 3-H$_{endo}$, *J*=12.5 Hz), 1.45 (d, 1H, 3′-H$_b$, *J*=14.7 Hz), 1.58–1.71 (m, 2H, 5-H$_{exo}$, 4-H), 2.06 (d, 1H, 3′-H$_a$, *J*=14.7 Hz), 2.12 (dt, 1H, 3-H$_{exo}$, *J*=12.5, 3.9 Hz), 2.44 (d, 1H, 1′-H$_b$, *J*=13.9 Hz), 2.68 (m, 4H, N–CH$_2$), 2.86 (d, 1H, 1′-H$_a$, *J*=13.9 Hz).

*3.9. (1*R,*2*S,*2′*R*)-2*-endo-*(1′-Diethylamino-2′-hydroxy-2′-methylpropyl)-1,7,7-trimethylbicyclo[2.2.1]-heptane-2-ol* **14**

Following the general procedure, 0.100 g (0.45 mmol) of **6** in 5 ml CH_3CN, 0.048 g (0.45 mmol) $LiClO_4$ and 0.160 g (2.25 mmol) Et_2NH were combined and stirred for 4 days at room temperature to give 0.120 g (89%) of **14**. MS (CI: NH_3) *m/z* (%): 298 ($[M+1]^+$, 100). Anal. calcd for $C_{18}H_{35}NO_2$ (297.5): C, 72.67; H, 11.86; N, 4.71; found: C, 72.31; H, 11.68; N, 4.58. $[\alpha]_D^{20}$: −5.9 (*c*=1.08, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 K): δ=0.82 (s, 3H, 9-H), 0.84 (s, 3H, 10-H), 0.91–1.05 (m, 1H, 5-H$_{endo}$), 1.01 (t, 6H, N–C–CH_3, *J*=7.1 Hz), 1.09 (s, 3H, 8-H), 1.20–1.40 (m, 2H, 6-H), 1.23 (s, 3H, 4′-H), 1.56 (d, 1H, 3′-H$_b$, *J*=14.0 Hz), 1.59–1.69 (m, 2H, 5-H$_{exo}$, 4-H), 1.60 (d, 1H, 3-H$_{endo}$, *J*=13.0 Hz), 1.94 (d, 1H, 3′-H$_a$, *J*=14.0 Hz), 2.08 (dt, 1H, 3-H$_{exo}$, *J*=13.2, 4.1 Hz), 2.29 and 2.41 (AB-system, 2H, 1′-H, *J*=13.9 Hz), 2.66 (m, 4H, N–CH_2).

*3.10. (1*R,*2*R,*2′*S*)-2*-exo-*(1′-Diethylamino-2′-hydroxypropyl)-1,3,3-trimethylbicyclo[2.2.1]heptane-2-ol* **15**

Following the general procedure, 0.200 g (0.95 mmol) of **7** in 5 ml CH_3CN, 0.102 g (0.95 mmol) $LiClO_4$ and 0.350 g (4.75 mmol) Et_2NH were combined and stirred for 3 days at room temperature to give 0.203 g (75%) of **15**. MS (CI: NH_3) *m/z* (%): 298 ($[M+1]^+$, 100). Anal. calcd for $C_{17}H_{33}NO_2$ (283.4): C, 72.05; H, 11.74; N, 4.94; found: C, 71.92; H, 11.39; N, 4.74. $[\alpha]_D^{20}$: +22.6 (*c*=1.07, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 K): δ=0.86–0.98 (m, 1H, 6-H$_{exo}$), 0.98–1.08 (m, 1H, 7-H$_{anti}$), 0.99 (s, 3H, 10-H), 1.01 (s, 3H, 8-H), 1.02 (t, 6H, N–C–CH_3, *J*=7.1 Hz), 1.05 (s, 3H, 9-H), 1.31–1.44 (m, 1H, 5-H$_{exo}$), 1.46–1.51 (m, 1H, 7-H$_{syn}$), 1.51 (dd, 1H, 3′-H$_{anti}$, *J*=14.7, 8.8 Hz), 1.58–1.61 (m, 1H, 4-H), 1.64 (dd, 1H, 3′-H$_{gauche}$, *J*=14.7, 2.0 Hz), 1.68–1.79 (m, 1H, 5-H$_{endo}$), 2.07–2.18 (m, 1H, 6-H$_{endo}$), 2.22 (dd, 1H, 1′-H$_{anti}$, *J*=12.7, 10.3 Hz), 2.41 (dd, 1H, 1′-H$_{gauche}$, *J*=12.7, 3.4 Hz), 2.49 (dq, 2H, N–CH_2, *J*=13.5, 7.1 Hz), 2.62 (dq, 2H, N–CH_2, *J*=13.5, 7.1 Hz), 3.93 (dddd, 1H, 2′-H, *J*=10.3, 8.8, 3.4, 2.0 Hz).

*3.11. (1*R,*2*R,*2′*R*)-2*-exo-*(1′-Diethylamino-2′-hydroxy-2′-methylpropyl)-1,3,3-trimethylbicyclo[2.2.1]-heptane-2-ol* **16**

Following the general procedure, 0.190 g (0.86 mmol) of **8** in 10 ml CH_3CN, 0.090 g (0.86 mmol) $LiClO_4$, and 0.310 g (4.30 mmol) Et_2NH were combined and stirred for 36 h at 50°C to give 0.115 g (45%) of **16**. MS (CI: NH_3) *m/z* (%): 298 ($[M+1]^+$, 100). Anal. calcd for $C_{18}H_{35}NO_2$ (297.5): C, 72.67; H, 11.86; N, 4.71; found: C, 72.52; H, 11.35; N, 4.89. $[\alpha]_D^{20}$: −15.4 (*c*=1.35, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 K): δ=0.94 (s, 3H, 8-H), 0.94–1.05 (m, 1H, 6-H$_{exo}$), 0.95 (s, 3H, 9-H), 1.02 (t, 6H, N–C–CH_3, *J*=7.1 Hz), 1.10–1.16 (m, 1H, 7-H$_{anti}$), 1.12 (s, 3H, 10-H), 1.16 (s, 3H, 4′-H), 1.28–1.42 (m, 1H, 5-H$_{exo}$), 1.45–1.50 (m, 1H, 7-H$_{syn}$), 1.56 (m, 1H, 4-H), 1.65–1.76 (m, 1H, 5-H$_{endo}$), 1.81 and 1.94 (AB-system, 2H, 3′-H, *J*=15.4 Hz), 2.00–2.17 (m, 1H, 6-H$_{endo}$), 2.41 (s, 1H, 1′-H), 2.68 (dq, 2H, N–CH_2, *J*=13.9, 7.1 Hz), 2.75 (dq, 2H, N–CH_2, *J*=13.9, 7.1 Hz).

*3.12. 3,5,6,6-Tetramethyl-4-oxatricyclo[5.2.1.0^{1,5}]-deca-3-methyl(*N,N*-diethyl)ammonium perchlorate* **21**

Following the general procedure, 0.100 g (0.45 mmol) of **6** in 5 ml CH_3CN, 0.048 g (0.45 mmol) $LiClO_4$ and 0.160 g (2.25 mmol) Et_2NH were combined and stirred for 10 h at 50°C. The mixture was treated with 2 N HCl and extracted with Et_2O. Evaporation of the washed (H_2O) and dried (Na_2SO_4)

ether extract yielded 0.075 g (46%) of **21**. The acidic layer was made alkaline with 2 N NaOH and extracted with Et_2O to give 0.023 g (17%) of **14**. MS (CI: NH_3) *m/z* (%): 280 {[(M–ClO_4)+1]$^+$, 100}. Anal. calcd for $C_{18}H_{34}NO_5Cl$ (379.9): C, 58.76; H, 9.30; N, 3.81; found: C, 55.05; H, 8.83; N, 4.02. ^{1}H NMR ($CDCl_3$, 300 K): δ=0.93 (s, 1H, 15-H), 0.99 (s, 3H, 14-H), 1.04 (s, 3H, 13-H), 1.08–1.12 (m, 1H, 10-H_{anti}), 1.33 (t, 3H, N–C–CH_3, *J*=7.3 Hz), 1.42 (t, 3H, N–C–CH_3, *J*=7.3 Hz), 1.21–1.51 (m, 3H, 9-H_{endo}, 8-H_{exo}, 9-H_{exo}), 1.56–1.69 (m, 1H, 8-H_{endo}), 1.61 (s, 3H, 11-H), 1.69–1.80 (m, 1H, 7-H), 1.86 and 1.96 (AB-system, 2H, 2-H, *J*=13.2 Hz), 2.09–2.23 (m, 1H, 10-H_{syn}), 3.03 (dd, 1H, 12-H_{anti}, *J*=13.5, 9.1 Hz), 3.14 (dd, 1H, 12-H_{gauche}, *J*=13.5, 2.7 Hz), 3.30 (dq, 2H, N–CH_2, *J*=11.7, 7.3 Hz), 3.45 (m, 1H, N–C$H_2$$CH_3$), 3.68 (m, 1H, N–C$H_2$$CH_3$), 7.57 (br. s, NH).

*3.13. 3,5,6,6-Tetramethyl-4-oxatricyclo[5.2.1.0^{1,5}]-deca-3-methyl(*N,N*-diethyl)amine **20***

A solution of **21** (0.026 g, 0.07 mmol) was dissolved in hot water (2 ml), containing KCl (0.01 g, 0.14 mmol). This solution was made alkaline with 2 N NaOH and extracted with Et_2O. Evaporation of the washed (H_2O) and dried (Na_2SO_4) ether extract yielded 0.018 g (93%) of amine **20**. ^{1}H NMR ($CDCl_3$, 300 K): δ=0.92 (s, 3H, 15-H), 0.92–1.02 (m, 1H, 10-H_{anti}), 0.97 (t, 6H, N–C–CH_3, *J*=7.1 Hz), 1.02 (s, 6H, 14-H, 13-H), 1.21–1.43 (m, 3H, 9-H, 8-H_{exo}), 1.35 (s, 3H, 11-H), 1.53–1.61 (m, 1H, 8-H_{endo}), 1.67–1.70 (m, 1H, 7-H), 1.69 (d, 1H, 2-H_b, *J*=12.7 Hz), 1.89 (d, 1H, 2-H_a, *J*=12.7 Hz), 2.16–2.25 (m, 1H, 10-H_{syn}), 2.36 and 2.46 (AB-system, 2H, 12-H, *J*=13.7 Hz), 2.60 (dq, 4H, N–CH_2, *J*=13.1, 7.1 Hz).

3.14. General procedure for the addition of diethylzinc to benzaldehyde

A solution of the ligand **9**–**16** (0.08 mmol) in toluene or hexane (6 ml) was cooled to 10°C and diethylzinc (1.1 M, 3.86 ml, 4.25 mmol in toluene or 1.0 M, 4.25 ml, 4.25 mmol in hexane) was added. The mixture was stirred for 0.5 h and cooled to −20°C. The benzaldehyde (0.29 ml, 0.30 g, 2.83 mmol) was added and the mixture allowed to warm slowly to room temperature and then stirred until completion of the reaction, monitored by TLC. The reaction mixture was quenched with saturated NH_4Cl solution (20 ml), then extracted with petroleum ether and the organic layer was then dried (Na_2SO_4). After evaporation of the solvent the residue was chromatographed and distilled to afford pure 1-phenyl-1-propanol.

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