

# Chiral Camphor-Based 1,3- and 1,4-Amino Alcohols and Aminodiols as Ligands for Diethylzinc Addition to Aldehydes

Olusegun B. Olubanwo<sup>1\*</sup>, James A. Golen<sup>1</sup>, Arnold L. Rheingold<sup>2</sup>, Vesa Nevalainen<sup>1,3</sup>

<sup>1</sup>Department of Chemistry and Biochemistry, University of Massachusetts Dartmouth, North Dartmouth, USA

<sup>2</sup>Department of Chemistry and Biochemistry, University of California San Diego, La Jolla, USA

<sup>3</sup>Chemveda Life Sciences, Weymouth, USA

Email: \*dele.olubanwo@umassd.edu

**How to cite this paper:** Olubanwo, O.B., Golen, J.A., Rheingold, A.L. and Nevalainen, V. (2018) Chiral Camphor-Based 1,3- and 1,4-Amino Alcohols and Aminodiols as Ligands for Diethylzinc Addition to Aldehydes. *International Journal of Organic Chemistry*, 8, 240-263.

<https://doi.org/10.4236/ijoc.2018.82018>

**Received:** April 25, 2018

**Accepted:** June 19, 2018

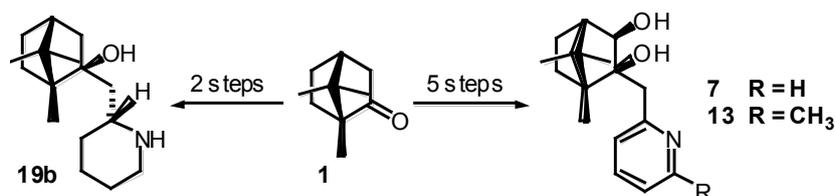
**Published:** June 22, 2018

Copyright © 2018 by authors and Scientific Research Publishing Inc. This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).  
<http://creativecommons.org/licenses/by/4.0/>



## Abstract

Syntheses of (1*R*,2*S*,3*R*,4*S*)-1,7,7-trimethyl-2-pyridin-2-ylmethylbicyclo[2.2.1]heptane-2,3-diol (**7**), (1*R*,2*S*,3*R*,4*S*)-1,7,7-trimethyl-2-[(6-methyl)-pyridin-2-ylmethyl-bicyclo[2.2.1]heptane-2,3-diol (**13**), and (1*R*,2*S*,2'*R*,4*R*)-1,7,7-trimethyl-2-piperidin-2-ylmethyl-bicyclo[2.2.1]heptan-2-ol (**19b**) from commercially available (*d*)-camphor (**1**) are described. Key steps of the syntheses involved substrate-controlled diastereoselective alkylation and platinum oxide-catalyzed hydrogenation reactions. These compounds, and other intermediate amino alcohols in their syntheses, were successfully utilized as ligands in enantioselective diethyl zinc (Et<sub>2</sub>Zn) addition to benzaldehyde with moderate enantioselectivity.



## Keywords

Ligand, Enantioselective, Amino Alcohol, Aminodiols, (+)-Camphor

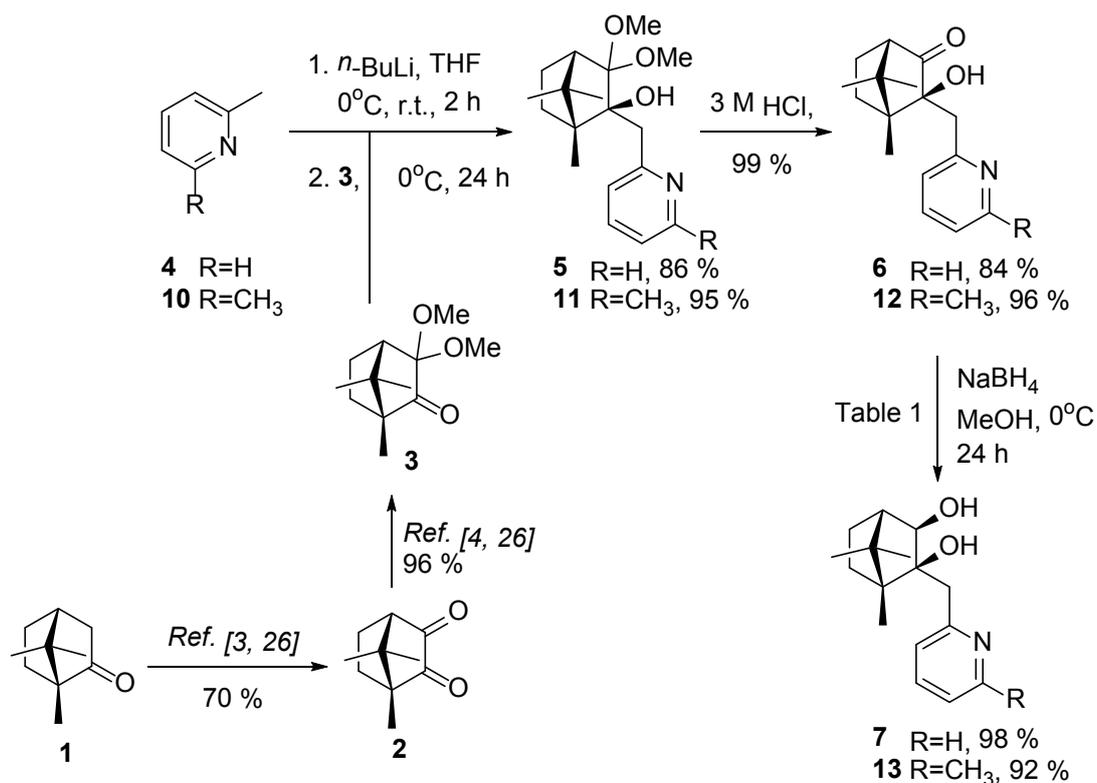
## 1. Introduction

Chiral amino alcohols are common precursors to many functional molecules [1]. One of the most extensively studied case is the catalytic enantioselective synthesis of chiral secondary alcohols using a chiral amino alcohol ligand capable of

forming a chelate with zinc. In a favorable case, the chelate is capable of catalyzing enantioselective additions of organozincs to aldehydes [2]. The first ligand, (*S*)-leucinol, used to catalyze the addition of diethylzinc ( $\text{Et}_2\text{Zn}$ ) to benzaldehyde gave moderate enantioselectivity (49%) as reported by Oguni and Omi in 1984 [3]. Since then series of 1,2-amino alcohols [5]-[14] have been reported for this transformation with moderate to excellent enantioselectivity [5]-[14]. However, the use of 1,3- and 1,4-amino alcohols [15]-[24] has been barely investigated. Herein, in continuation of our ongoing research on the design and synthesis of new chiral ligands for asymmetric reactions [25], we are reporting syntheses of new amino alcohols and amino diols derived from (+)-camphor. The utility of the new ligands for the addition of  $\text{Et}_2\text{Zn}$  to benzaldehyde was also studied briefly.

## 2. Result and Discussion

The synthesis of diols **7** and **13** began with the conversion of camphor **1** to 3,3-dimethoxy ketal **3** using known methodologies [4] [26] [27] (**Scheme 1**). First, commercially available (*d*)-camphor **1**, was oxidized to camphorquinone **2**, using selenium oxide in acetic anhydride under refluxing condition [26]. The obtained camphorquinone **2** was refluxed with trimethyl orthoformate in methanol in the presence of catalytic amount of *p*-TsOH affording 3,3-dimethoxy ketal **3** in high yield [4] [26].



**Scheme 1.** Synthesis of amino diols **7** and **13**. Compounds **2** and **3** were synthesized using established protocols [3] [4] [26].

To synthesize amino diol **7** (Scheme 1), dimethoxy ketal **3** was treated with lithiated picoline **4** in THF at 0°C. This resulted in diastereoselective addition of the lithiated picoline to the dimethoxy ketal **3** rendering amino alcohol **5** as brown oil in 86% yield. Subsequent deprotection of the dimethoxy ketal group of **5** by acid hydrolysis gave aminohydroxyketone **6** as a white solid in 84% yield.

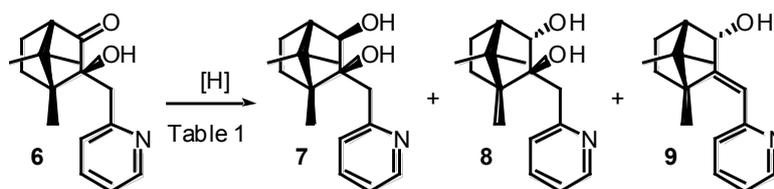
Regioselective hydride reduction of aminohydroxy ketone **6** to amino diol **7** was studied using six reducing agents (Table 1). We assume that the amino diol **8** (not isolated) was the main by-product of these reduction reactions, because the hydride could only approach the carbonyl carbon either from the *Re* or the *Si* side.

Reduction with sodium borohydride in diethyl ether gave high selectivity comparable to that obtained with sterically demanding tetramethylamino borohydride (Table 1, entries 1 and 5), albeit in lower yield. With sodium borohydride in methanol (entry 2), an increase in yield and decrease in selectivity was observed. Lithium aluminum hydride gave unexpectedly a poor yield and selectivity (entry 3).

Interestingly, reduction of **6** with aluminum isopropoxide (entry 4) led to a predominant formation of compound **9**. This compound **9** probably formed through the precursor enone since the *endo*-configuration at C3 of **9** was expected due to the MPV conditions used.

In order to confirm the stereochemistry of the hydroxyl group at C3 of **7**, the flash-column-chromatography-purified amino diol was recrystallized from a solvent pair system of methanol/water (50%). A single crystal X-ray analysis

**Table 1.** Hydride reductions of aminohydroxyketone **6**.



Entry	[H]	Solvent	Temperature (°C)	Time (hr)	*Yield (%)	<sup>b</sup> Ratio 7:8:9
1	NaBH <sub>4</sub>	Ether	0	24	90.4	24:1:0
2	NaBH <sub>4</sub>	Methanol	0	24	97.0	17:1:0
3	LiAlH <sub>4</sub>	Ether	25	24	69.0	6:1:0
4	Al( <i>i</i> -Pr) <sub>3</sub>	Toluene	Reflux	24	87.5	1:2:11 <sup>c</sup>
5	N(CH <sub>3</sub> ) <sub>4</sub> BH <sub>4</sub>	Methanol	25	12	97.0	25:1:0
6	Selectride	THF	25	24	98.0	20:1:0
7	BH <sub>3</sub> S(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	25	72	70.0	15:1:0

<sup>a</sup>After flash column chromatography. <sup>b</sup>Based on <sup>1</sup>H NMR signals of methyl groups before purification by flash column chromatography. <sup>c</sup>Based on the <sup>1</sup>H- and <sup>13</sup>C-NMR analysis of the crude product.

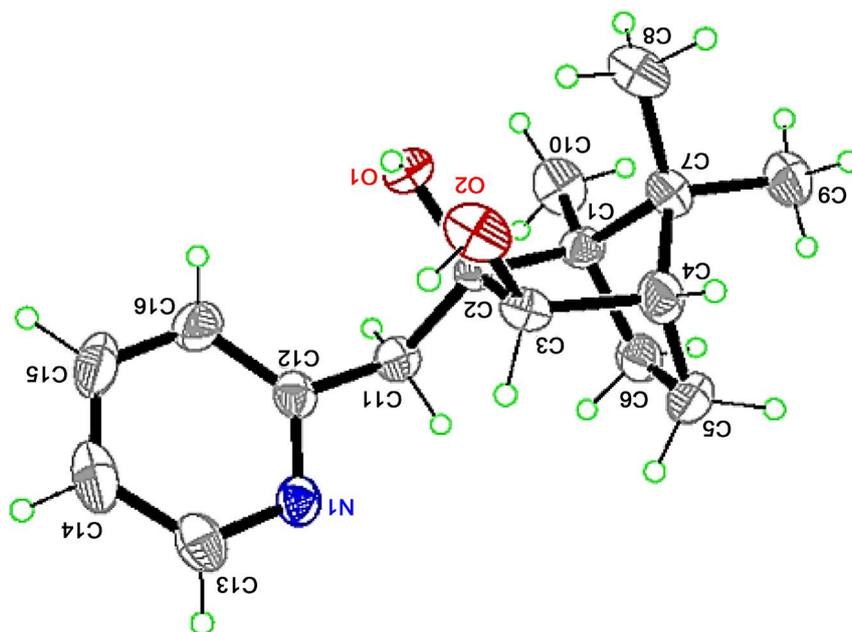
confirmed the stereochemistry of the alcohol functional groups at *C2* and *C3* of amino diol **7** to be as shown in **Figure 1** [28].

With the synthetic route to amino diol **7** and the *2S* and *3R* stereochemistry at *C2* and *C3* successfully established, amino diol **13** was synthesized using the same methodology (**Scheme 1**) from 2,6-lutidine and the 3,3-dimethoxy ketal **3**. Thus, nucleophilic addition of lithiated 2,6-lutidine, **10** to dimethoxy ketal **3** afforded amino alcohol **11** in 95% yield. Hydrolysis of **11** using 3 M HCl gave aminohydroxyketone **12** in 96% yield. Subsequent hydride reduction of the aminohydroxyl ketone with sodium borohydride in methanol at 0°C afforded amino diol **13** in 92% yield.

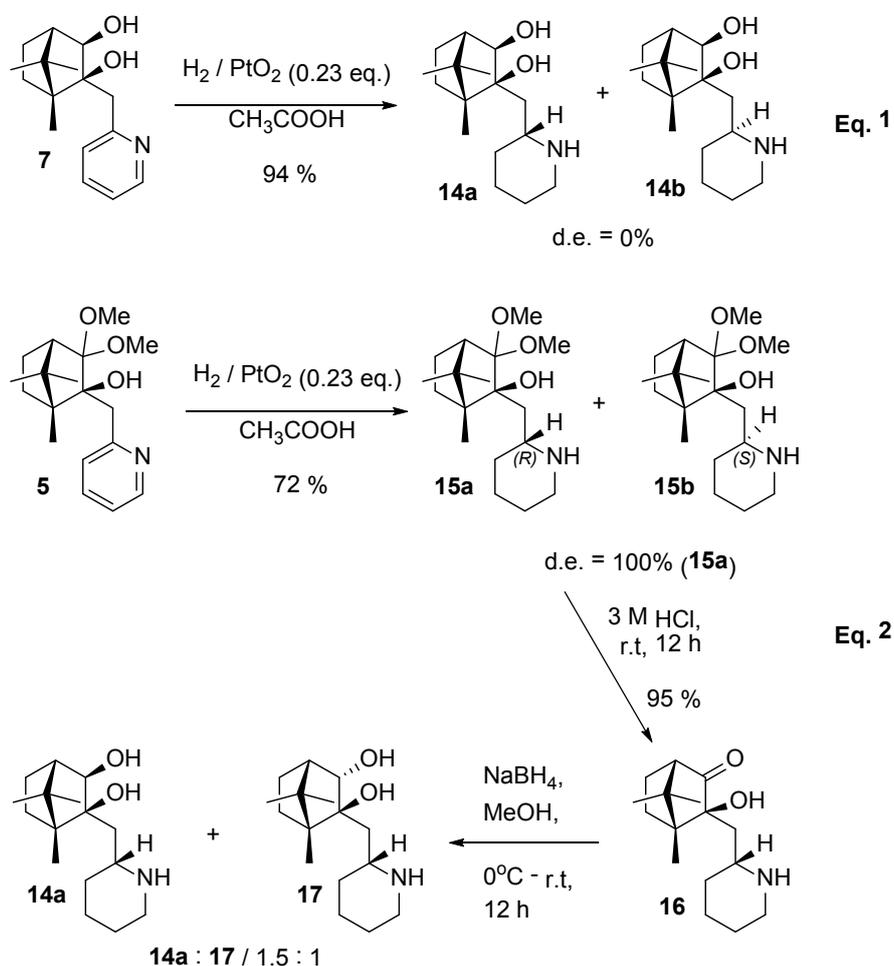
This family of ligands obtained was expanded by subjecting some of the amino alcohol members to catalytic hydrogenation using Adam's catalyst in acetic acid. We envisaged that the already established stereocenters in the substrates will induce some sort of asymmetry at the new chiral center that will be formed upon hydrogenation of the pyridine ring. Thus, amino diol **7** was first subjected to catalytic hydrogenation in a Parr hydrogenator using platinum oxide in acetic acid (**Scheme 2**, Equation (1)). To our disappointment both epimers **14a** and **14b** (**Scheme 2**, Equation (1)) of the expected piperidine product were formed in almost equal amount, and proved to be very difficult to separate by chromatography, crystallization or resolution using chiral resolving agents (tartaric acid and camphorsulfonic acid).

The epimers were also derivatized by alkylation and acylation of the secondary amine, but the corresponding products had closely similar  $R_f$  values. Consequently, another route to these epimers was investigated.

To this end amino alcohol **5** was hydrogenated using platinum oxide (Adam's



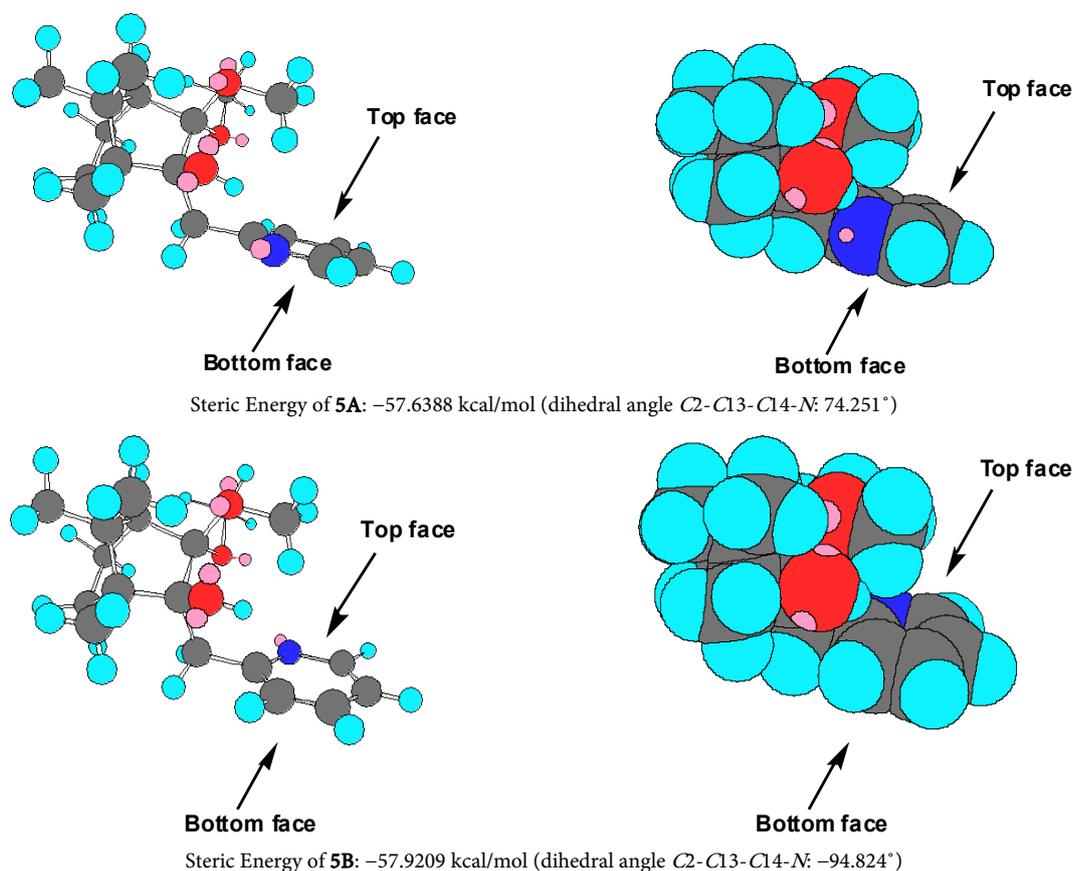
**Figure 1.** X-Ray crystal structure of amino diol **7**.<sup>9</sup> Unit Cell Dimensions:  $a = 7.140(2) \text{ \AA}$ ;  $\alpha = 90^\circ$ ;  $b = 18.794(6) \text{ \AA}$ ;  $\beta = 90^\circ$ ;  $c = 21.357(6) \text{ \AA}$ ;  $\gamma = 90^\circ$ .<sup>9</sup>



**Scheme 2.** Catalytic hydrogenations using Adam's catalyst.

catalyst) in glacial acetic acid and interestingly, the corresponding product, assumably **15a** (Scheme 2, Equation (2)), was obtained diastereoselectively in 72% yield (as confirmed by the  $^1\text{H}$  NMR of the crude product, based on the signals of the methyl groups). This is apparently because of the presence of the dimethoxy group at *C3* of the camphor skeleton. The space filling molecular model [29] representations (Figure 2) of two most stable rotamers of **5** show that the top side of the pyridine is sterically more hindered than the bottom side. Since the mechanism [30] of hydrogenation involves coordination of the organic substrate onto the metal through the  $\pi$ -bonds, it is therefore reasonable to expect that the hydrogenation of **5** would occur on the bottom face of **5A** or **5B** (Figure 2).

Since the bottom face of **5A** and **5B** is clearly more accessible than the top one, the formation of **15a** likely involves **5A**. Since **5A** and **5B** are almost equally stable (Figure 2), the origin of favor of **5A** over **5B** could be a solvent effect. This reduction is conducted in glacial acetic acid. Since acetic acid is very polar and capable of hydrogen bonding to the nitrogen of pyridine ring and such interactions are more favorably present in **5A** than in **5B** (nitrogen buried under the 3,3-dimethoxy ketal group), this conformer, **5A**, could be more stabilized over



**Figure 2.** Molecular models (cylindrical bonds and space filling types) of lowest-energy rotamers (solvent effects omitted) of compound **5**.

**5B.** Furthermore, in **5B** the fatty part of the pyridine ring sticks far out into polar solvent (unfavorable interactions) whereas in **5A** the fatty part is partially shielded by methyl groups of the dimethoxyketal group (stabilizing hydrophobic interactions).

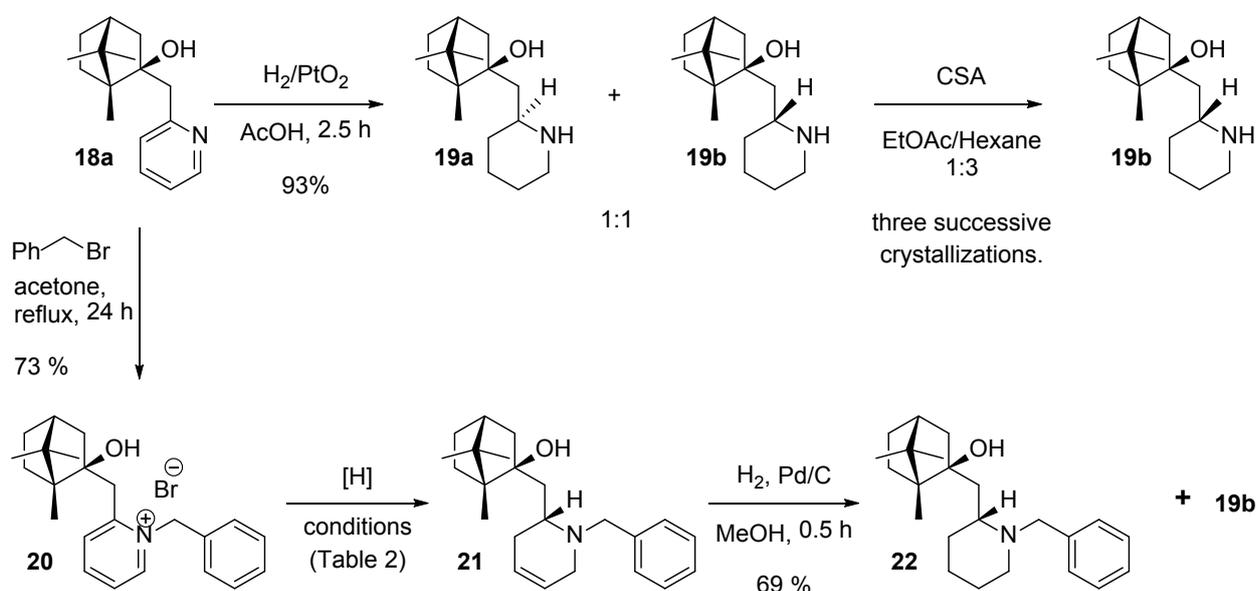
Hydrogenation of **5** to **15a** was succeeded by acid-catalyzed hydrolysis of the amino alcohol **15a** to aminohydroxy ketone **16** in 95% yield. Hydride reduction of this aminohydroxy ketone afforded amino diols **14a** and **17** in 1.5:1 ratio (**Scheme 2**, Equation (2)). Unfortunately, efforts to separate these diastereomers proved unsuccessful too.

Literature search showed that neither these amino diols, nor **16** have been synthesized or reported before. The closest ligand reported with isoborneol-picolinyl skeleton are **18a** and isoborneol-6-methylpicolinyl **18b** [31] [32]. Also, the catalytic hydrogenation of **18a** has been reported [31] [32] and the product **19** (as a mixture of **19a** and **19b**) was characterized on the basis of a melting point only. To this end, we decided to investigate catalytic hydrogenation of **18a** with the intention of using the corresponding anticipated amino alcohol as a catalyst in asymmetric reactions.

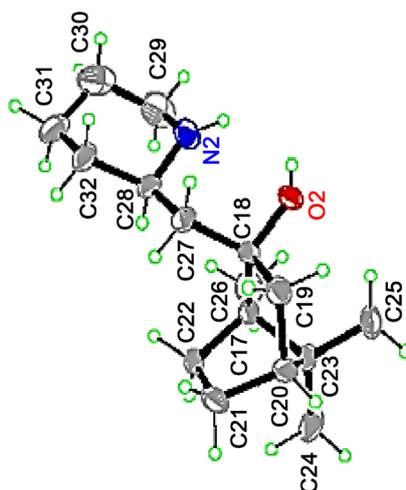
Thus, amino alcohol **18a** was synthesized according to Xu *et al.* [31]. This amino alcohol was then subjected to catalytic hydrogenation using Adam's reagents

and a mixture of epimers **19a** and **19b** was obtained. The epimers were resolved by successive recrystallization of their camphorsulfonic acid (CSA) salts (**Scheme 3, Figure 3**). To circumvent the cumbersome recrystallization step, another reductive route to **19b** was adopted. Thus, a quaternary ammonium salt **20** was easily synthesized [33] by refluxing **18a** with benzyl bromide in acetone (**Scheme 3**). This quaternary ammonium salt was then subjected to hydride reduction [34] [35] using different reducing agents and conditions (**Table 2**) to obtain **21** (**Scheme 3, Figure 4**). Reduction of **20** with sodium borohydride [34] and tetramethylammonium borohydride both gave excellent yields (**Table 2**). For example, sodium borohydride afforded almost complete conversion to **21** (**Table 2, entries 1 and 2**).

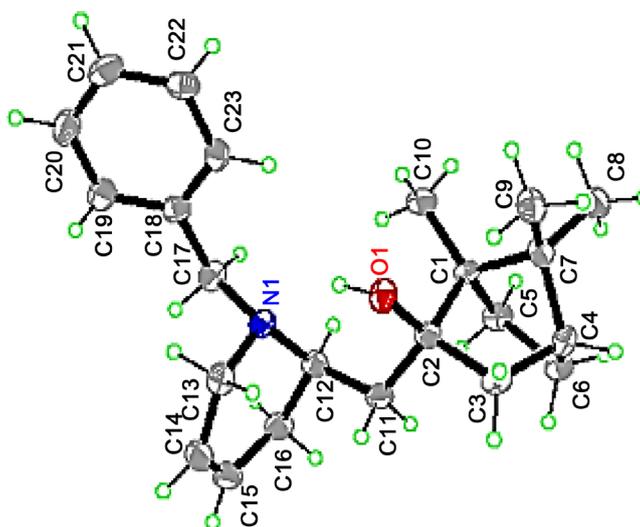
The absolute chirality of the new stereogenic center at *C12* of **21** was also



**Scheme 3.** Synthesis of 2-(2-Piperidylmethyl) boreneols **19a** and **19b**.



**Figure 3.** X-Ray structure of **19b** [28]. Unit Cell Dimensions:  $a = 15.9379(15)$  Å;  $b = 16.8811(16)$  Å;  $c = 22.605(2)$  Å [28].

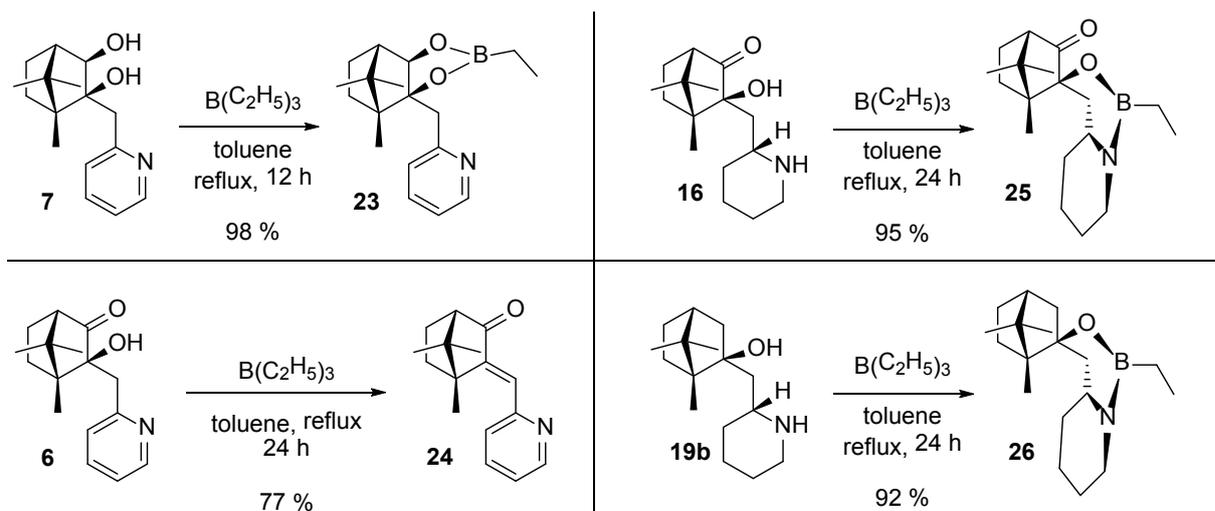


**Figure 4.** X-Ray structure of **21** [28] Unit Cell Dimension:  $a = 11.7681(16) \text{ \AA}$   $b = 6.9494(10) \text{ \AA}$ ;  $c = 11.9268(17) \text{ \AA}$  [28].

**Table 2.** Hydride reductions of quaternary ammonium salt **20**.

Entry	[H]	Solvent	Temp. [ $^{\circ}\text{C}$ ]	Time [hours]	*Yield of <b>21</b> %
1	$\text{NaBH}_4$	MeOH	0 – r.t.	2	98
2	$\text{NaBH}_4$	MeOH	-10	24	99
3	$\text{N}(\text{CH}_3)_4\text{BH}_4$	MeOH	-10	24	94
4	$\text{N}(\text{CH}_3)_4\text{BH}_4$	MeOH	0 – r.t.	7	88

\*After column chromatography.



**Scheme 4.** Reaction of ligands **7**, **6**, **16** and **19b** with triethyl borane.

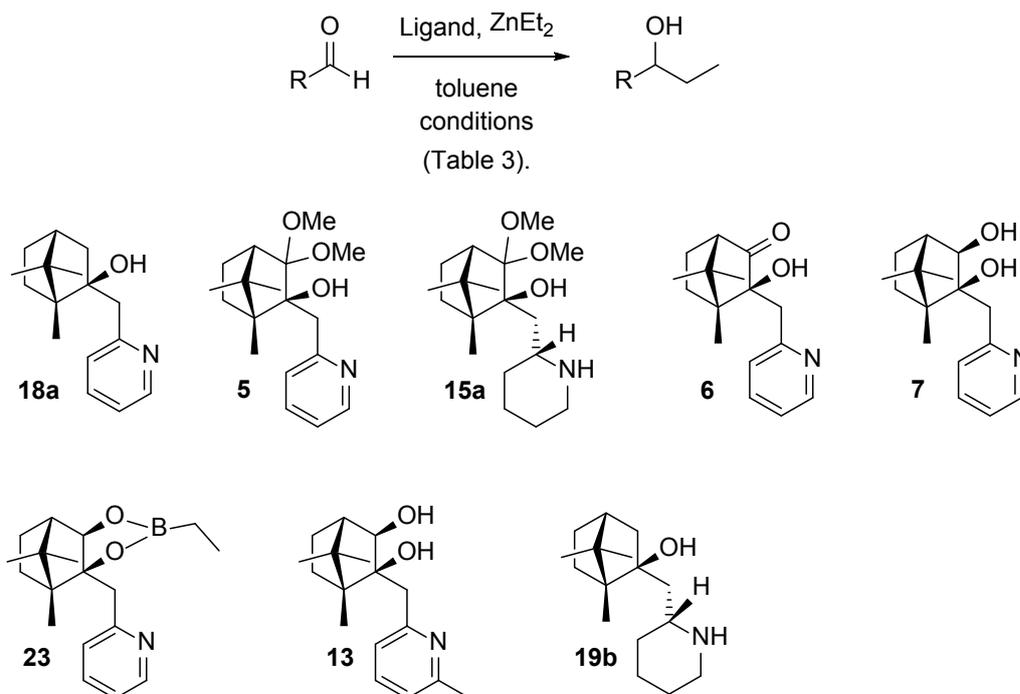
unambiguously assigned by X-ray structure of **21** (Figure 4). Subsequent hydrogenation of **21** in methanol, catalyzed by palladium on carbon in 30 minutes afforded **22** and **19b**. Presumably all **22** could have been converted to **19b** if a longer reaction time had been used.

Since new chiral Lewis acids are always interesting, we decided to briefly probe the synthesis boron chelates of some our new amino alcohols (**Scheme 4**). Thus toluene solutions of **7**, **16**, and **19b** with triethylborane were refluxed for 24 h (**Scheme 4**) respectively. Boron chelates **23**, **25** and **26** were obtained in a very clean reaction in high yields: 98%, 95% and 92% respectively. An attempt was also made to obtain a boron chelate of **6**. However, when the reaction was stopped after 48 h, the main product turned out to be **24** (**Scheme 4**). This supports the above-discussed mechanism of formation of **9** (**Table 1**, entry 4) through enone **24**.

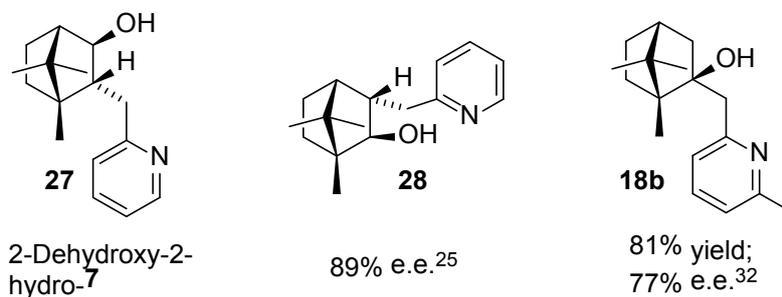
### 3. Enantioselective Addition of Diethylzinc to Aldehydes: A Brief Screening of the Ligands

A brief screening of the new ligands was conducted using a catalytic enantioselectively additions of  $\text{Et}_2\text{Zn}$  to aldehydes as a “probe”. Various reaction conditions (**Scheme 5**) were used with benzaldehyde as a model substrate. This very preliminary work aimed on detecting ligands which could have any promise instead of optimizing reaction conditions. Results are shown in **Table 3**.

First compounds with one free hydroxyl group (*i.e.* **5**, **6**, **15a** and **19b**) were examined. In the case of compound **18a** our results [entry 1] [34% e.e. of the (*R*)-alcohol] matched what has been published (38% e.e. of the same (*R*)-alcohol) earlier [31]. Interestingly, the 6-methyl substituent of the picolinyl group of **18b** (**Figure 5**) has a major impact on the enantioselectivity of this reaction. Compound **18b** has been reported to give 77% e.e. of the same (*R*)-alcohol with benzaldehyde as a substrate [32].



**Scheme 5.** Ligand for enantioselective diethyl zinc addition to aldehydes.



**Figure 5.** Picoline-based [25] and lutidine-based bidentate ligands [32].

The only experiment conducted using 20 mol.% of amino alcohol **19b** with 5 eq.  $\text{Et}_2\text{Zn}$  (relative to benzaldehyde) gave (*R*)-1-phenylpropanol as the dominating product with an enantiomeric excess of 45% (Table 3, entry 13). This is about 10%-units higher than the corresponding value of **18a** (entry 1). An *N*-alkylated derivative of **19b** could give a higher enantiomeric excess.

The reaction of  $\text{Et}_2\text{Zn}$  with benzaldehyde and **5** was conducted using 2 eq. of  $\text{Et}_2\text{Zn}$  (relative to the aldehyde) at 0°C in the presence of 20, 10, and 5 mol.% of **5** (Table 3, entries 2 - 4). Unfortunately, the enantioselectivities were very poor. The 3,3-dimethoxy ketal group probably rendered the OH group at *C2* too crowded (in between two quaternary centers in **5**).

When compound **6** was used as a ligand, a slightly better enantioselectivities were observed, but now with the (*S*)-1-phenylpropanol of the dominating product in 19% - 22% e.e. (Table 3, entries 5 and 6). This is interesting as it seems as if space near *C3* of the bornane skeleton of compound **18a** would be in close contact with the active center of the catalyst. In this light a proper modification of the substitution pattern at *C3* could lead to a discovery of a highly enantioselective ligand.

Ligands **7** and **13** turned out to be clearly more enantioselective than **5**, **6** or **18a**. Using **7**, the best enantioselectivity obtained was 67% (with benzaldehyde) as a substrate whereas with **13**, the best enantioselectivity obtained was 77% (with *p*-chlorobenzaldehyde). Since **7** performed clearly better than **18a**, one could conclude that the 3-OH group may play a more important role in this reaction than the 2-OH group does. In that light **27**, 2-dehydroxy-2-hydro derivative of **7** (Figure 5), could still be a better catalyst than **7**. This conclusion is supported by results published earlier [25]. Ligand **28**, which is structurally closely similar to **7**, catalyzed this reaction (Scheme 5) with 89% e.e. and in a high yield [25]. Therefore, in this group of 1,4- and 1,3-amino alcohols, the former seems to give significantly better enantioselectivity. In the case of hybrid ligands, such as **7**, the enantioselectivities seem to fall in between those of the parents (as the 2-OH group is there lowering the enantioselectivity). Therefore, further studies aiming on better enantioselectivities of derivatives of **18a** should focus on derivatives of **27** and **28** instead of related 1,3-aminoalcohols (such as **18**), or hybrid compounds (e.g. **7**). However, in the case of derivatives of **18b** the contrary may apply: **18b** has been reported [32] to give 77% e.e. with benzalde-

hyde in the same reaction in which **18a** gives only 34% e.e. Indeed, compound **13**, which is a 3-hydroxy derivative of **18b**, gave (*R*)-1-phenylpropanol with a lower enantioselectivity than **18b** has been reported [32] to do. This could indicate that the diethylzinc coordinated to the ethylzinc alkoxide of 3-hydroxyl group of **13** is only lowering the enantioselectivity of the reaction occurring at the diethylzinc coordinated to the ethylzinc alkoxide of 2-hydroxyl group of **13**. A similar conclusion was drawn earlier by Pale *et al.* [32] when they studied closely related amino diols **18b** and *C*<sub>2</sub>-symmetric **18c** (Figure 6). Compound **18b** (77% e.e. and 81% yield of the (*R*)-1-phenylpropanol) turned out to be a slightly better catalyst [32] than **18c** (75% e.e. and 78% yield of the same (*R*)-alcohol), which gave rise to a conclusion that only one hydroxyl group of **18c** at the time is part of the active center of the catalysts. In this light different hydroxyl groups of amino diols **7** and **13** could be important for their catalytic performance and enantioselectivity.

Diethylzinc additions can be sensitive to reaction conditions. Interestingly, 20 mol.% of **7** gave a lower enantiomeric excess (57%, entry 11) than obtained using 10 mol.% of **7** (67%, entry 12). Based on the results the performance of ligand **13** (entries 14 and 15) does not significantly differ from that of **7**. We chose to use 5 eq. of Et<sub>2</sub>Zn (relative to the aldehyde) with both amino diols **7** and **13** to ensure that Et<sub>2</sub>Zn-ligand ratio would be high enough to keep both OH groups of amino diols **7** and **13** as zinc ethoxides each coordinated to one Et<sub>2</sub>Zn molecule through their lone pairs of the alkoxide oxygens. This is what is needed for an amino alcohol, such as DAIB, to be an active catalyst [1] [36] [37] [38] [39] [40]. With **18a** we used only 2 eq. to reproduce the literature [31] data. Also in the case of the related reactions of ligand **28** the Et<sub>2</sub>Zn-ligand ratio of 2.2 : 1 was sufficient to render 1-phenylpropanol in high yield and in 89% e.e. [25]. As regarding the reaction mechanism, with 5 eq. of Et<sub>2</sub>Zn (relative to the aldehyde) all plausible Lewis basic sites on ligands **7** and **13** should be coordinated to zinc. The resulting Zn-saturated complex could bind an aldehyde molecule leading to the formation of adducts such as **A** or **A'** (Scheme 6). An intramolecular ethyl transfer reaction from zinc to the aldehyde in **A/A'** could lead to the formation of **B/B'**. A reaction of **B/B'** with Et<sub>2</sub>Zn should regenerate the catalyst and renders the (*R*)-product as an ethylzinc alkoxide (Scheme 6) which subsequently would be stabilized as a Et<sub>2</sub>Zn adduct. This mechanism discussed above (Scheme 6) is similar to the one proposed earlier for DAIB [1] [36] [37] [38] [39] [40].

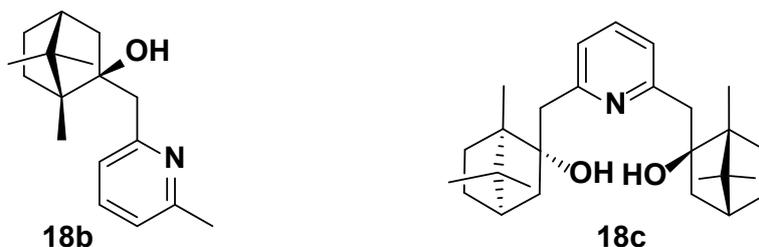


Figure 6. Lutidine-based bidentate and tridentate ligands [32].

A few substrates other than benzaldehyde were briefly studied using ligand **13** (Table 3, entries 16 - 19). Interestingly, in the case of reaction of *p*-chlorobenzaldehyde catalyzed by a zinc chelate of **13** the product was the (*S*)-1-(4'-chlorophenyl)-propanol in 77% e.e. (Table 3, entry 16). Also 2-naphthaldehyde gave (*S*)-alcohol but in much lower enantioselectivity (entry 17). This is somewhat peculiar as ligand **18b** has been reported to give right the same 77% e.e. with benzaldehyde but the product was reported<sup>12b</sup> to be (*R*)-1-phenylpropanol. This may suggest that the mechanism of this reaction is more complex than that described in Scheme 6 or in the literature [1] [36] [37] [38] [39] [40]. Aggregation of the catalyst could play a role.

## 4. Experimental

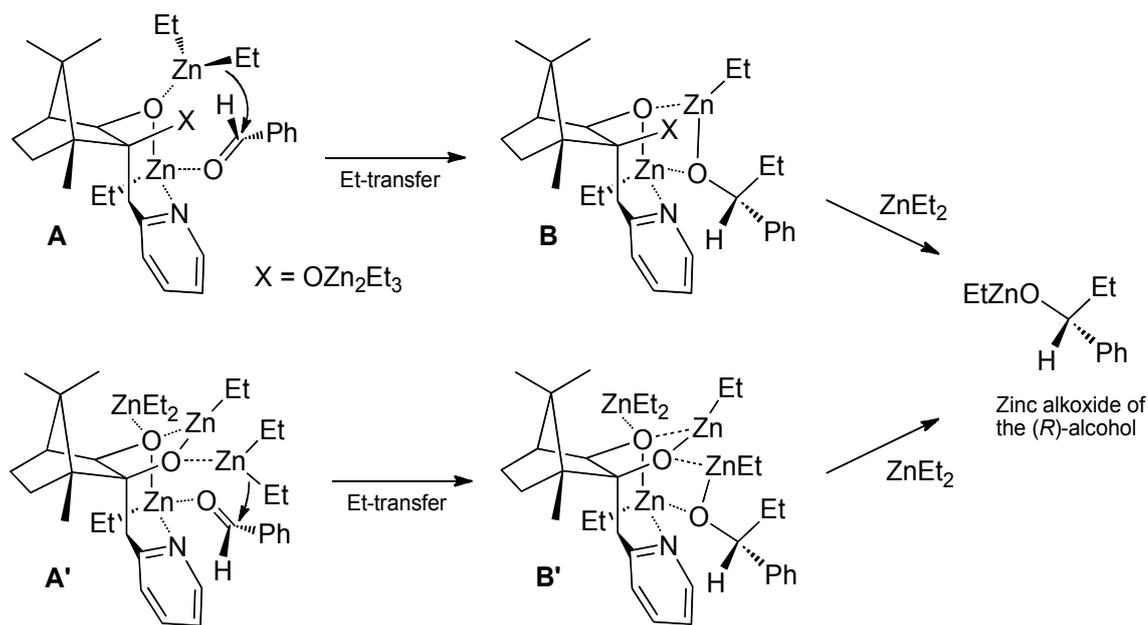
### General

<sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Spectrospin and Bruker

**Table 3.** Enantioselective addition of diethylzinc to aldehydes.

Entry	Aldehyde	Ligand	Amount of ligand [mol-%]	Et <sub>2</sub> Zn Eq./T [#/'°C]	Time [hr]	Yield [%]	e.e. [%] <sup>a</sup>	R/S <sup>d</sup>
1	Benzaldehyde	<b>18a</b>	10	2/0	24	98	34	R
2	Benzaldehyde	<b>5</b>	20	2/0	24	63	12	R
3	Benzaldehyde	<b>5</b>	10	2/0	12	90	9 <sup>b</sup>	R
4	Benzaldehyde	<b>5</b>	5	2/0	12	80	1 <sup>b</sup>	R
5	Benzaldehyde	<b>6</b>	20	2/0	24	40	19 <sup>b</sup>	S
6	Benzaldehyde	<b>6</b>	10	2/0	24	85	22 <sup>b</sup>	S
7	Benzaldehyde	<b>15a</b>	10	3/0	24	75	- <sup>c</sup>	- <sup>c</sup>
8	3,4,5-Trimethoxybenzaldehyde	<b>23</b>	5	3/0	24	98	-	-
9	Benzaldehyde	<b>7</b>	5	4/r.t.	24	11	15	R
10	Benzaldehyde	<b>7</b>	10	4/r.t.	24	17	7	R
11	Benzaldehyde	<b>7</b>	20	5/0	24	85	57	R
12	Benzaldehyde	<b>7</b>	10	5/0	24	94	67	R
13	Benzaldehyde	<b>19b</b>	20	5/0	24	88	45	R
14	Benzaldehyde	<b>13</b>	10	5/-10	24	90	61	R
15	Benzaldehyde	<b>13</b>	5	5/-10	24	75	36	R
16	<i>p</i> -Chlorobenzaldehyde	<b>13</b>	5	5/0	24	95	77	S
17	2-Naphthaldehyde	<b>13</b>	5	5/0	24	60	15	S
18	3,4,5-Trimethoxybenzaldehyde	<b>13</b>	5	5/0	24	37	2	S
19	Benzaldehyde	<b>13</b>	5	2.5/r.t.	24	21	9	R

<sup>a</sup>Determined using Chiralcel OD column, hex./IPA 95:5, 0.7 mL/min. The literature e.e. value for ligand **18a** (20 mol%, entry 1) was 38.1% [31]. <sup>b</sup>Determined using Chiralcel AD column, hex./IPA 95:5, 1.0 mL/min. <sup>c</sup>Not determined. <sup>d</sup>See Appendix for the original chromatogram. *R/S* configuration assigned as described in the literature [25].



**Schem 6.** **A** and **A'**: Diethylzinc derivative of **7** (4 eq. of  $\text{ZnEt}_2$ ) in complex with benzaldehyde. **B** and **B'**: A complex of the zinc alkoxide product before the regeneration (1 eq. of  $\text{ZnEt}_2$ ) of the catalyst.

(300 MHz/52MM) and (75 mMHz) spectrometer respectively in  $\text{CDCl}_3$ . For  $^1\text{H}$  NMR spectra  $\text{CDCl}_3$  (with chemical shift of 7.27 ppm) was used as an internal reference. In the case of  $^{13}\text{C}$  NMR spectra, the internal reference was also  $\text{CDCl}_3$  with chemical shift of 77.0 ppm. Column chromatography was carried out on Fluka Chemika Silica gel 60 (ratios of eluent systems are given under each experimental procedure). Thin layer chromatography (TLC) was done with plastic-back Alltech sorbent silica gel. FTIR was performed on a Bruker Vector 22 instrument. Mass Spectral data were obtained at the University of Massachusetts Amherst Mass Spectrometry Facility which is supported, in part, by the National Science Foundation. All chemicals and solvents were used as supplied, except THF, which was distilled over sodium. All liquid aldehydes were washed with sodium bicarbonate, extracted, dried over magnesium sulfate and distilled prior to use.

Acetic anhydride, butyl lithium (in cyclohexane) and lithium aluminum hydride were obtained from Aldrich Chemical; Trimethylorthoformate, *p*-toluenesulfonic acid, sodium borohydride, ammonium chloride and aluminum triisopropoxide were purchased from ACROS Organics; Magnesium sulfate and sulfuric acid were obtained from Fisher Chemicals; Ethyl acetate, methanol, hexane, dichloromethane and hydrochloric acid (ACS reagent grade) were bought from Pharmco; (+)-Camphor was obtained from Eastman Organic Chemicals; Selenium oxide bought from Alfa Aesar; Sodium hydroxide (pelletes) purchased from J.T. Baker Chemical Co.; Silica gel 60 obtained from Fluka Chemika; Diethyl ether (anhydrous) was bought from Mallinckrodt Chemicals; 2-Picoline was purchased from Avocado research chemicals; Toluene from DESMO Chemicals; Platinum oxide from Engelhard; Acetic acid (glacial) from EM Science and Te-

trahydrofuran from OmniSolv (EM).

**(1*R*,2*S*,4*S*)-3,3-Dimethoxy-1,7,7-trimethyl-2-pyridin-2-ylmethylbicyclo[2.2.1]heptan-2-ol, 5.**

To 2-picoline (0.7 mL, 7.07 mmol) in a 100 mL 2-neck flask under nitrogen was added anhydrous THF (30.0 mL). The reaction flask was cooled to 0 °C and 2.0 M *n*-BuLi (3.8 mL, 7.47 mmol) in cyclohexane was added over 15 minutes under vigorous stirring. The reaction mixture was allowed to warm up to room temperature and then stirred for 1 hour. The mixture was cooled back to 0 °C and a solution of (1*R*,4*S*)-3,3-Dimethoxy-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-one, **3** (1.50 g, 7.07 mmol), in THF (20.0 mL) was added over 15 minutes. After 24 hours, the reaction mixture was neutralized with saturated aqueous ammonium chloride, THF layer was separated and the water layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined, washed with brine, dried over magnesium sulfate and evaporated to dryness. The residue was purified by column chromatography to afford pure (1*R*,2*S*,4*S*)-3,3-dimethoxy-1,7,7-trimethyl-2-pyridin-2-ylmethylbicyclo[2.2.1]heptan-2-ol, **5** (1.36 g, 6.09 mmol) as a dark brown oil in 86.1% yield.  $R_f$  0.51 (silica, hexane/ethyl acetate 5:1),  $[\alpha]_{589\text{nm}}^{29.6} = +89.6$  (conc. = 1.2 g/100 mL, CHCl<sub>3</sub>). <sup>1</sup>H NMR,  $\delta$  (ppm): 0.59 (s, 3H), 0.81 (s, 3H), 1.28 (s, 3H), 1.48 - 1.56 (m, 3H), 1.80 (s, 1H), 2.8 (d,  $J = 13.8$  Hz, 1H), 2.88 (s, 3H), 3.06 (s, 3H), 3.15 (d,  $J = 10.5$  Hz, 1H), 6.65 (s, 1H), 7.09 (t,  $J_1 = J_2 = 5.1$  Hz, 1H), 7.25 (d,  $J = 4.2$  Hz, 1H), 7.58 (t,  $J = 7.6$  Hz, 1H), 8.36 (d,  $J = 4.3$  Hz, 1H). <sup>13</sup>C NMR,  $\delta$  (ppm): 11.32 (CH<sub>3</sub>), 20.90 (CH<sub>2</sub>), 22.36 (CH<sub>3</sub>), 22.51 (CH<sub>3</sub>), 29.78 (CH<sub>2</sub>), 39.17 (CH<sub>2</sub>), 47.13 (C), 49.88 (CH<sub>3</sub>), 50.72 (CH<sub>3</sub>), 52.57 (CH), 54.14 (C), 86.40 (C), 110.47 (C), 121.17 (CH), 125.78 (CH), 136.56 (CH), 147.21 (CH), 161.25 (C).

**(1*S*,3*S*,4*R*)-3-Hydroxy-4,7,7-trimethyl-3-pyridin-2-ylmethylbicyclo[2.2.1]heptan-2-one, 6.**

To (1*R*,2*S*,4*S*)-3,3-dimethoxy-1,7,7-trimethyl-2-pyridin-2-ylmethylbicyclo[2.2.1]heptan-2-ol, **5** (13.26 g, 43.4 mmol) in a 250 mL single-neck reaction flask with magnetic stirring bar was added 3 M HCl (80.0 mL) at room temperature and stirred for 24 hours. Reaction mixture was neutralized with 3 M aqueous sodium hydroxide until the pH was basic. The mixture was extracted with ethyl acetate (3 × 50 mL). Organic extracts were dried over magnesium sulfate and evaporated to dryness. Purification of the residue by flash column chromatography afforded pure (1*S*,3*S*,4*R*)-3-hydroxy-4,7,7-trimethyl-3-pyridin-2-ylmethylbicyclo[2.2.1]heptan-2-one, **6** (11.13 g, 42.9 mmol) in 83.8% yield, as a white solid.  $R_f$  0.22 (silica, hexane/ethyl acetate 5:1);  $[\alpha]_{589\text{nm}}^{28.5} = -93.7$  (conc. = 1.23 g/100 mL, CHCl<sub>3</sub>), mp = 125.3 °C - 130.5 °C. <sup>1</sup>H NMR,  $\delta$  (ppm): 0.59 (s, 3H), 0.93 (s, 3H), 1.12 (s, 3H), 1.54-1.57 (m, 1H), 1.73 (d,  $J = 6.8$  Hz, 1H), 1.69 (d,  $J = 4.1$  Hz, 2H), 1.96 - 2.05 (m, 1H), 2.22 (d,  $J = 5.4$  Hz, 1H), 2.87 (d,  $J = 14.7$  Hz, 1H), 3.07 (d,  $J = 14.7$  Hz, 1H), 7.18 (d,  $J = 7.7$  Hz, 1H), 7.22 (d,  $J = 5.0$  Hz, 1H), 7.66 (ddd,  $J_1 = 7.7$  Hz,  $J_2 = 7.7$  Hz,  $J_3 = 1.8$  Hz, 1H), 8.46 (d,  $J = 4.9$  Hz, 1H); <sup>13</sup>C NMR,  $\delta$  (ppm): 10.5 (CH<sub>3</sub>), 19.0 (CH<sub>3</sub>), 22.1 (CH<sub>2</sub>), 22.3 (CH<sub>3</sub>), 30.3 (CH<sub>2</sub>), 40.2 (CH<sub>2</sub>), 46.7 (C), 52.7 (C), 58.9 (CH), 80.7 (C), 121.9 (CH), 124.3 (CH), 137.1 (CH),

147.9 (CH), 159.1 (C), 218.3 (C=O).

**(1*R*,2*S*,3*R*,4*S*)-1,7,7-Trimethyl-2-pyridin-2-ylmethylbicyclo[2.2.1]heptane-2,3-diol, 7.**

To a solution of (1*S*,3*S*,4*R*)-3-hydroxy-4,7,7-trimethyl-3-pyridin-2-ylmethylbicyclo[2.2.1]-heptan-2-one, **6** (1.80 g, 6.94 mmol) in methanol (50.0 mL) in a reaction flask was added, in small portions, sodium borohydride (2.63 g, 69.4 mmol) at 0°C under vigorous stirring. The reaction proceeded for 24 hours at 0°C. Water (5 mL), 10% aqueous sodium hydroxide (100.0 mL), and ethanol (50.0 mL) were then added and stirred for 30 minutes. The ethanol was evaporated and the reaction mixture was extracted using ethyl acetate (3 × 30 mL). Combined organic extracts were dried over magnesium sulfate and evaporated to dryness affording colorless oil (1.77 g, 6.76 mmol) in 99% crude yield. The crude product was purified by flash column chromatography to afford pure (1*R*,2*S*,3*R*,4*S*)-1,7,7-trimethyl-2-pyridin-2-ylmethyl-bicyclo[2.2.1]heptane-2,3-diol, **7** (1.76 g, 6.75 mmol, 97% yield) as a white solid upon evaporation of solvent.  $R_f$  0.49 (silica, hexane/ethyl acetate 2:1).  $[\alpha]_{589\text{nm}}^{21.9} = +39.47$  (conc. = 0.76 g / 100 mL, CHCl<sub>3</sub>); mp = 82.8-85.5°C. <sup>1</sup>H NMR,  $\delta$  (ppm): 0.66 (s, 3H), 0.82 (s, 3H), 1.18 (s, 3H), 1.42 (d,  $J = 5.0$  Hz, 1H), 1.45 (d,  $J = 3.8$  Hz, 1H), 1.68 (s, 1H), 1.78 (d,  $J = 4.5$  Hz, 1H), 2.04 (s, 1H), 2.95 (d,  $J = 14.4$  Hz, 1H), 3.06 (d,  $J = 14.3$  Hz, 1H), 3.50 (s, 1H), 7.22 (d,  $J = 7.8$  Hz, 2H), 7.67 (ddd,  $J_1 = 9.5$  Hz,  $J_2 = 9.5$  Hz,  $J_3 = 1.8$  Hz, 1H), 8.45 (d,  $J = 4.2$  Hz, 1H). <sup>13</sup>C NMR,  $\delta$  (ppm): 10.8 (CH<sub>3</sub>), 22.1 (CH<sub>3</sub>), 22.6 (CH<sub>3</sub>), 24.7 (CH<sub>2</sub>), 30.1 (CH<sub>2</sub>), 42.9 (CH<sub>2</sub>), 49.3 (C), 50.9 (CH), 52.3 (C), 81.9 (C), 82.4 (CH), 121.8 (CH), 124.5 (CH), 137.3 (CH), 147.9 (CH), 159.4 (C).

**(1*R*,2*S*,4*S*)-3,3-Dimethoxy-1,7,7-trimethyl-2-(6-methyl-pyridin-2-ylmethyl)-bicyclo[2.2.1]-heptan-2-ol, 11.**

To 2,6-lutidine (0.55 mL, 4.71 mmol) in a 100 mL 2-neck flask under nitrogen was added anhydrous THF (40.0 mL). The reaction flask was cooled to 0°C and 2.0 M *n*-BuLi (2.6 mL, 5.18 mmol) in cyclohexane was added over 15 minutes. The reaction mixture was allowed to warm up to room temperature and kept at that temperature with stirring for 2 hour. The mixture was cooled back to 0°C and a solution of (1*R*,4*S*)-3,3-dimethoxy-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-one, **3** (1.50 g, 7.07 mmol) in dry THF (10.0 mL) was added over 15 minutes. After 24 hours, the reaction mixture was neutralized with saturated aqueous ammonium chloride, the THF layer was separated and the water layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined, washed with brine, dried over magnesium sulfate and evaporated to dryness. The residue was purified by column chromatography to afford pure (1*R*,2*S*,4*S*)-3,3-dimethoxy-1,7,7-trimethyl-2-(6-methyl-pyridin-2-ylmethyl)-bicyclo[2.2.1]heptan-2-ol, **11** (1.42 g, 4.45 mmol) in 95% yield. NMR data of this intermediate were not taken. It was simply hydrolyzed to **12**.

**(1*S*,3*S*,4*R*)-3-Hydroxy-4,7,7-trimethyl-3-(6-methyl-pyridin-2-ylmethyl)-bicyclo[2.2.1]-heptan-2-one, 12.**

To (1*R*,2*S*,4*S*)-3,3-dimethoxy-1,7,7-trimethyl-2-(6-methyl-pyridin-2-ylmethyl)-

bicyclo[2.2.1]-heptan-2-ol, **11** (1.02 g, 3.73 mmol) in a 250 mL single-neck reaction flask with magnetic stirring bar was added 3 M HCl (50.0 mL) at room temperature and stirred for 24 hours. Reaction mixture was neutralized with 3 M aqueous sodium hydroxide until the pH was basic. The mixture was extracted with ethyl acetate (3 × 30 mL). Organic extracts were dried over magnesium sulfate and evaporated to dryness. Purification of the residue by flash column chromatography afforded pure (1*S*,3*S*,4*R*)-3-hydroxy-4,7,7-trimethyl-3-(6-methyl-pyridin-2-ylmethyl)-bicyclo[2.2.1]heptan-2-one, **12** (0.97 g, 3.55 mmol) in 95.8% yield, as a white solid.  $R_f$  0.6 (silica, hexane/ethyl acetate 1:1).  $^1\text{H}$  NMR,  $\delta$  (ppm): 0.59 (s, 3H), 0.92 (s, 3H), 1.12, (s, 3H), 1.46 - 1.55 (m, 1H), 1.67 - 1.73 (m, 2H), 1.93 - 2.04 (m, 1H), 2.20 (d,  $J = 5.3$  Hz, 1H), 2.50 (s, 3H), 2.81 (d,  $J = 14.7$  Hz, 1H), 3.02 (d,  $J = 14.7$  Hz, 1H), 6.96 (d,  $J = 7.6$  Hz, 1H), 7.05 (d,  $J = 7.7$  Hz, 1H), 7.53 (t,  $J_1 = J_2 = 7.7$  Hz, 1H).  $^{13}\text{C}$  NMR,  $\delta$  (ppm): 10.5 (CH<sub>3</sub>), 19.0 (CH<sub>3</sub>), 22.0 (CH<sub>2</sub>), 22.3 (CH<sub>3</sub>), 24.1 (C), 30.3 (CH<sub>2</sub>), 40.0 (CH<sub>2</sub>), 46.6 (C), 52.6 (CH), 59.0 (CH<sub>3</sub>), 80.6 (C-OH), 121.0 (CH), 121.4 (CH), 137.3 (CH), 156.9 (C), 158.2 (C), 218.2 (C=O).

**(1*R*,2*S*,3*R*,4*S*)-1,7,7-Trimethyl-2-(6-methyl-pyridin-2-ylmethyl)-bicyclo[2.2.1]heptane-2,3-diol, 13.**

To a solution of (1*S*,3*S*,4*R*)-3-hydroxy-4,7,7-trimethyl-3-(6-methyl-pyridin-2-ylmethyl)bicyclo-[2.2.1]heptan-2-one, **12** (0.39 g, 1.43 mmol) in methanol (10.0 mL) in a reaction flask was added, in small portions, sodium borohydride (0.54 g, 14.29 mmol) at 0°C with vigorous stirring. The reaction proceeded for 24 hours at 0°C, then water (5 mL), 10% aqueous sodium hydroxide (30 mL), and ethanol (20 mL) were added and the mixture was stirred for 30 minutes. The ethanol was evaporated and the reaction mixture was extracted using ethyl acetate (3 × 20 mL). Combined organic extracts were dried over magnesium sulfate and evaporated to dryness affording colorless oil (0.39 g, 1.42 mmol) quantitatively. The crude product was purified by flash column chromatography to afford pure (1*R*,2*S*,3*R*,4*S*)-1,7,7-trimethyl-2-(6-methyl-pyridin-2-ylmethyl)bicyclo[2.2.1]heptane-2,3-diol, **13** (0.36 g, 1.3 mmol, 92% yield) as a white solid upon evaporation of solvent.  $R_f$  0.6 (silica, hexane/ethyl acetate 1:1).  $^1\text{H}$  NMR,  $\delta$  (ppm): 0.66 (s, 3H), 0.82 (s, 3H), 0.99 - 1.09 (m, 1H), 1.19 (s, 3H), 1.35 - 1.45 (m, 2H), 1.68 - 1.77 (m, 2H), 2.51 (s, 3H), 2.89 (d,  $J = 14.3$  Hz, 1H), 3.01 (d,  $J = 14.3$  Hz, 1H), 3.44 (s, 1H), 6.99 (d,  $J = 7.6$  Hz, 1H), 7.03 (d,  $J = 7.8$  Hz, 1H), 7.53 (t,  $J_1 = J_2 = 7.7$  Hz, 1H).  $^{13}\text{C}$  NMR,  $\delta$  (ppm): 10.8 (CH<sub>3</sub>), 22.1 (CH<sub>3</sub>), 22.5 (CH<sub>3</sub>), 24.1 (CH<sub>3</sub>), 24.6 (CH<sub>2</sub>), 30.1 (CH<sub>2</sub>), 42.5 (CH<sub>2</sub>), 49.3 (C), 50.9 (CH), 52.2 (C), 81.9 (C-OH), 82.3 (CH-OH), 121.3 (CH), 137.5 (CH), 156.8 (C), 158.5 (C).

**(1*R*,2*S*,4*S*,2'*R*)-3,3-Dimethoxy-1,7,7-trimethyl-2-piperidin-2'-ylmethylbicyclo[2.2.1]heptan-2-ol, 15a.**

To a solution of (1*R*,2*S*,4*S*)-3,3-dimethoxy-1,7,7-trimethyl-2-pyridin-2-ylmethylbicyclo[2.2.1]-heptan-2-ol, **5** (1.18 g, 3.87 mmol) in acetic acid (6.0 mL) inside a Parr hydrogenation bottle was added PtO<sub>2</sub> (0.20 g, 0.87 mmol). The bottle was evacuated and then filled with hydrogen to a pressure of 44 psi. The hy-

drogenation reaction was conducted for 2 h, after which the solid PtO<sub>2</sub> catalyst was filtered off using celite and the solution was neutralized with 3 M aqueous sodium hydroxide until pH was very basic (pH = 10). The obtained solution was extracted with ethyl acetate (3 × 30 ml), dried over magnesium sulfate, and evaporated to dryness to obtain a dark brown viscous liquid (1.14 g, 3.68 mmol, 95% crude yield). Upon purification by flash column chromatography (eluent: hexane/EtOAc 1:1), (1*R*,2*S*,4*R*,2'*R*)-3,3-dimethoxy-1,7,7-trimethyl-2-piperidin-2'-ylmethyl-bicyclo[2.2.1]-heptan-2-ol, **15a**, (0.87 g, 2.78 mmol) was obtained in 72% yield, as a light-brown powder. R<sub>f</sub> 0.4 (silica, hexane/ethyl acetate 1:1). <sup>1</sup>H NMR, δ (ppm): 0.74 (s, 3H), 0.79 (s, 3H), 1.02 - 1.22 (m, 2H), 1.26 (s, 3H), 1.33 (d, *J* = 8.9 Hz, 1H), 1.38 - 1.66 (m, 3H), 1.78 (d, *J* = 4.6 Hz, 2H), 1.81 (d, *J* = 1.3 Hz, 1H), 2.46 (ddd, *J*<sub>1</sub> = *J*<sub>2</sub> = 3.0 Hz, *J*<sub>3</sub> = 13.8 Hz, 1H), 2.96 (dd, *J*<sub>1</sub> = 2.1 Hz, *J*<sub>2</sub> = 6.2 Hz, 2H), 3.11 (s, 3H), 3.40 (s, 3H). <sup>13</sup>C NMR, δ (ppm): 10.8 (CH<sub>3</sub>), 20.5 (CH<sub>2</sub>), 22.2 (CH<sub>3</sub>), 22.4 (CH<sub>3</sub>), 24.5 (CH<sub>2</sub>), 27.1 (CH<sub>2</sub>), 29.2 (CH<sub>2</sub>), 34.2 (CH<sub>2</sub>), 36.8 (CH<sub>2</sub>), 45.4 (CH<sub>2</sub>), 46.7 (C), 50.2 (CH<sub>3</sub>), 50.6 (CH<sub>3</sub>), 52.8 (CH), 54.0 (C), 55.4 (CH), 86.9 (C), 110.8 (C).

**(1*S*,3*S*,4*R*,2'*R*)-3-Hydroxy-4,7,7-trimethyl-3-piperidin-2'-ylmethylbicyclo[2.2.1]heptan-2-one, 16.**

A solution of (1*R*,2*S*,4*R*,2'*R*)-3,3-dimethoxy-1,7,7-trimethyl-2-piperidin-2'-ylmethylbicyclo[2.2.1]heptan-2-ol, **15a** (0.185 g, 0.59 mmol) in aqueous 3 M HCl (3.0 mL) was stirred in a 25 mL reaction flask for 24 h at room temperature. The mixture was then neutralized with 3 M aqueous sodium hydroxide until the pH was basic (pH = 10). The suspension thus obtained was extracted with ethyl acetate (3 × 15 mL). Combined organic extracts were dried over magnesium sulfate and evaporated to dryness. The residue was further purified by flash column chromatography to afford pure (1*S*,3*S*,4*R*,2'*R*)-3-hydroxy-4,7,7-trimethyl-3-piperidin-2'-ylmethylbicyclo[2.2.1]heptan-2-one, **16** (0.15 g, 0.56 mmol) in 95% yield, as a brown solid. R<sub>f</sub> 0.3 (silica, hexane/ethyl acetate 1:1). <sup>1</sup>H NMR, δ (ppm): 0.92 (s, 3H), 0.94 (s, 3H), 1.11 (s, 3H), 1.10 - 1.23 (m, 2H), 1.27-1.41 (m, 3H), 1.46 - 1.65 (m, 6H), 1.75 - 1.86 (m, 2H), 2.10 (d, *J* = 5.2 Hz, 1H), 2.66 (ddd, *J*<sub>1</sub> = 2.9 Hz, *J*<sub>2</sub> = 14.1 Hz, 2H), 3.02 (d, *J* = 13.4 Hz, 1H), 3.36 (t, *J* = 10.9 Hz, 1H). <sup>13</sup>C NMR, δ (ppm): 9.59 (CH<sub>3</sub>), 19.2 (CH<sub>3</sub>), 21.7 (CH<sub>2</sub>), 22.1 (CH<sub>3</sub>), 23.8 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>), 29.7 (CH<sub>2</sub>), 33.4 (CH<sub>2</sub>), 37.4 (CH<sub>2</sub>), 45.0 (CH<sub>2</sub>), 46.3 (C), 52.8 (C), 53.6 (CH), 59.9 (CH), 79.2 (C), 221.4 (C=O).

**(1*R*,2*S*,4*S*,2'*R*)-1,7,7-Trimethyl-2-piperidin-2'-ylmethyl-bicyclo[2.2.1]heptan-2-ol, 19b and (1*R*,2*S*,4*R*,2'*S*)-1,7,7-Trimethyl-2-piperidin-2'-ylmethyl-bicyclo[2.2.1]heptan-2-ol, 19a.**

A solution of (1*R*,2*S*,4*R*)-1,7,7-trimethyl-2-piperidin-2'-ylmethylbicyclo[2.2.1]heptan-2-ol, **18a** (1.0 g, 4.08 mmoles) in glacial acetic acid (6.0 mL) was placed in a hydrogenation bottle of Parr Hydrogenator and platinum oxide (0.2 g, 0.92 mmoles) was added. The bottle was placed in the designated area of the hydrogenation equipment and air was removed from the inside of the bottle before filling the bottle with hydrogen at a pressure of 35 psi. After 2.5 hours, the cata-

lyst was filtered off through celite and 10% aqueous sodium hydroxide (30 mL) was added to the reaction mixture. The suspension formed was extracted with ethyl acetate (3 × 20 mL), combined organic fractions were dried over magnesium sulfate and the solvent was evaporated to dryness affording white solid (0.958 g, 8.81 mmoles) in 93% yield (d.e. = 50% base on methyl signals). The components of the white solid were separated as follows: Combined crude products (from three repeated experiments) (2.95 g, 12.0 mmol), containing mixture of **19a** and **19b** was dissolved in ethyl acetate (6.0 mL) and hexane (2.0 mL) in a 13 mm × 100 mm Pyrex glass test tube. The obtained solution was warmed up in a hot water bath and D-(+)-10-camphorsulfonic acid (2.73 g, 12.0 mmol) was added. The solution was further warmed up in hot water bath until all the acid has dissolved. The test tube was taken out of the water bath and allowed to cool to room temperature. White crystals of the salt started to precipitate out of the solution after about 15 minutes, so the solution was allowed to stand at r.t. for about 2 hours. The solid crystalline material was separated from the mother liquor by filtration and recrystallized two more times (as described). The final crystals were dissolved in water (20.0 mL) and 3 M NaOH (50.0 mL) was added (pH = 10). Obtained suspension was extracted with ethyl acetate (3 × 20 mL), combined organic extracts dried over magnesium sulfate, filtered and evaporated to dryness to afford (1*R*,2*S*,4*S*,2'*R*)-1,7,7-trimethyl-2-piperidin-2'-ylmethylbicyclo[2.2.1]heptan-2-ol, **19b** (1.39 g, 5.5 mmol) as white solid in 47% yield. Comparison of NMR data (methyl signals) of the crude mixture and pure (1*R*,2*S*,4*S*,2'*R*)-1,7,7-trimethyl-2-piperidin-2'-ylmethyl-bicyclo[2.2.1]heptan-2-ol, **19b** revealed that **19b** is the major constituent of the mixture. mp = 71.5°C - 73°C,  $[\alpha]_{589\text{nm}}^{28.1} = +78.1$  (conc. = 0.38 g/100 mL, CHCl<sub>3</sub>).

<sup>1</sup>H NMR of (1*R*,2*S*,4*S*,2'*R*)-1,7,7-trimethyl-2-piperidin-2'-ylmethyl-bicyclo[2.2.1]heptan-2-ol, **19b** (major component),  $\delta$  (ppm): 0.82 (s, 3H), 0.96 (s, 3H), 0.99 - 1.03 (m, 1H), 1.08 (s, 3H), 1.17 (s, 1H), 1.24 (d,  $J = 3.6$  Hz, 2H), 1.28 - 1.33 (m, 1H), 1.34 - 1.47 (m, 2H), 1.49 - 1.52 (m, 1H), 1.54 - 1.58 (m, 2H), 1.61 (d,  $J_1 = 4.5$   $J_2 = 4.4$  Hz, 2H), 1.65 (d,  $J = 2.6$  Hz, 1H), 1.68 - 1.76 (m, 2H), 1.79 - 1.86 (m, 1H), 1.99 (t,  $J_1 = 4.0$  Hz,  $J_2 = 3.3$  Hz, 1H), 2.04 (dd,  $J_1 = 4.1$  Hz,  $J_2 = 3.8$  Hz, 1H), 2.52 (ddd,  $J_1 = J_2 = J_3 = 2.8$  Hz, 1H), 2.89 (tt,  $J_1 = 2.5$  Hz,  $J_2 = 10.7$  Hz, 1H), 3.02 (m, 1H). <sup>13</sup>C NMR of (1*R*,2*S*,4*S*,2'*R*)-1,7,7-trimethyl-2-piperidin-2'-ylmethyl-bicyclo[2.2.1]heptan-2-ol, **19b**,  $\delta$  (ppm): 12.1 (CH<sub>3</sub>), 20.9 (CH<sub>3</sub>), 21.2 (CH<sub>3</sub>), 24.7 (CH<sub>2</sub>), 27.1 (CH<sub>2</sub>), 27.2 (CH<sub>2</sub>), 30.6 (CH<sub>2</sub>), 34.2 (CH<sub>2</sub>), 44.9 (CH), 46.2 (CH<sub>2</sub>), 46.5 (CH<sub>2</sub>), 49.1 (CH<sub>2</sub>), 50.1 (C), 52.1 (C), 55.8 (CH), 81.1 (C-OH).

(1*R*,2*S*,4*R*,2'*S*)-1,7,7-trimethyl-2-piperidin-2'-ylmethyl-bicyclo[2.2.1]heptan-2-ol, **19a** <sup>1</sup>H NMR of **19a** (minor component: partial assignment of peaks from crude mixture by comparison with pure **19b**),  $\delta$  (ppm): 0.81 (s, 3H), 0.83 (s, 3H), 1.11 (s, 3H), 2.10 (dt,  $J_1 = 3.5$  Hz,  $J_2 = 12.7$  Hz, 1H), 2.57 (d,  $J = 2.8$  Hz, 1H), 2.62 (d,  $J = 2.6$  Hz, 1H), 2.78 (b, 1H), 2.93 (m, 1H). <sup>13</sup>C NMR of **19a**,  $\delta$  (ppm): 10.6, 21.0, 21.7, 27.0, 27.3, 30.0, 35.0, 43.1, 45.3, 45.6, 47.5, 52.2, 55.2, 81.2.

#### 1-Benzyl-2-((1*R*,2*S*,4*R*)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl

**methyl)-pyridinium bromide, 20.**

To a solution of (1*R*,2*S*,4*R*)-1,7,7-trimethyl-2-pyridin-2-ylmethylbicyclo[2.2.1]heptan-2-ol, **18** (1.03 g, 4.19 mmol) in acetone (10 mL) was added benzyl bromide (1.43 g, 8.38 mmol). The obtained solution was refluxed for 24 h and then allowed to cool back to room temperature. Solid precipitate that formed after cooling was filtered and rinsed three times with ethyl acetate (3 x 10 mL). 1-Benzyl-2-((1*R*,2*S*,4*R*)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylmethyl)pyridinium bromide, **20** was formed as white crystalline solid in 73% yield (1.27 g, 3.04 mmol). <sup>1</sup>H NMR,  $\delta$  (ppm): 0.89 (s, 3H), 0.99 (s, 3H), 1.06 (s, 3H), 1.29 - 1.37 (m, 1H), 1.43 - 1.54 (m, 1H), 1.71 - 1.78 (m, 1H), 1.87 (s, broad, 2H), 3.11 (d,  $J = 14.0$  Hz, 1H), 3.42 (d,  $J = 14.0$  Hz, 1H), 5.92 (d,  $J = 15.7$  Hz, 1H), 6.21 (d,  $J = 15.7$  Hz, 1H), 7.14 (d,  $J = 7.9$  Hz, 2H), 7.43 (m, 3H), 7.98 (t,  $J_1 = J_2 = 6.3$  Hz, 1H), 8.29 (d,  $J = 8.0$  Hz, 1H), 8.52 (t,  $J_1 = J_2 = 7.9$  Hz, 1H), 8.91 (d,  $J = 6.3$  Hz, 1H). The <sup>13</sup>C NMR was not taken for this intermediate.

**(1*R*,2*S*,4*R*)-2-(((2'*R*)-1'-Benzyl-1',2',3',6'-tetrahydropyridin-2'-yl)methyl)-1,7,7-trimethyl-bicyclo-[2.2.1]heptan-2-ol, 21.**

To a solution of 1-benzyl-2-((1*R*,2*S*,4*R*)-2-hydroxy-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl-methyl)pyridinium bromide, **20** (50 mg, 0.12 mmol) in methanol (3 mL) at  $-10^\circ\text{C}$  was added sodium borohydride (22.7 mg, 0.6 mmol) under vigorous stirring. The reaction was stirred at this temperature for 24 h and thereafter quenched with water (5 mL) and 20% aqueous NaOH (5 mL) with stirring for additional 15 minutes. Additional water (10 mL) was added to the reaction mixture and the obtained mixture was extracted with dichloromethane (3 x 15 mL). The organic extracts were dried over magnesium sulfate, the drying agent filtered and the solvent evaporated to afford golden-yellow solid. This solid was purified by flash column chromatography, using eluent system of hexane/ethyl acetate (6:1), (1*R*,2*S*,4*R*)-2-(((2'*R*)-1'-benzyl-1',2',3',6'-tetrahydropyridin-2'-yl)methyl)-1,7,7-trimethyl-bicyclo-[2.2.1]heptan-2-ol, **21** (40.8 mg, 0.11 mmol) in 98.9% yield as white solid. <sup>1</sup>H NMR,  $\delta$  (ppm): 0.83 (s, 3H), 1.01 (s, 3H), 1.11 (s, 3H), 1.23 - 1.37 (m, 2H), 1.39 - 1.56 (m, 2H), 1.61 - 1.65 (m, 1H), 1.68 - 1.71 (m, 1H), 1.73 - 1.83 (m, 2H), 2.04 (t,  $J_1 = 4.1$  Hz,  $J_2 = 3.0$  Hz, 1H), 2.08 (t,  $J_1 = 4.6$  Hz,  $J_2 = 2.8$  Hz, 1H), 2.11 (d,  $J = 2.9$  Hz, 1H), 2.34 (broad peak, 1H), 2.95 (broad peak, 1H), 3.33 (broad peak, 1H), 3.44-3.49 (m, 1H), 3.64 (d,  $J = 13.0$  Hz, 1H), 3.85 (d,  $J = 13.0$  Hz, 1H), 5.52 (m, 1H), 5.80 (m, 1H), 7.21-7.34 (m, 5H). <sup>13</sup>C NMR,  $\delta$  (ppm): 12.6, 21.0, 21.2, 25.5, 27.3, 30.7, 38.9, 41.8, 44.6, 45.1, 48.9, 50.5, 51.9, 55.3, 81.6, 123.5, 124.1, 127.1, 128.4, 128.8, 129.0, 129.1, 138.5.

**(1*R*,2*S*,6*R*,7*S*)-2-((4-Ethyl-1,10,10-trimethyl-3,5-dioxo-4-bora-tricyclo[5.2.1.0<sup>2,6</sup>]dec-2-yl)methyl)pyridine, 23.**

To a solution of (1*R*,2*S*,3*R*,4*S*)-1,7,7-trimethyl-2-pyridin-2-ylmethylbicyclo[2.2.1]heptane-2,3-diol, **7** (0.10 g, 0.383 mmol) in toluene (1.0 mL) in a 25 mL two-neck round-bottomed flask was added 1 M triethyl borane (0.38 mL, 0.383 mmol) and the solution was refluxed for 12 hours. Excess solvent was evapo-

rated to afford (1*R*,2*S*,6*R*,7*S*)-2-((4-ethyl-1,10,10-trimethyl-3,5-dioxa-4-boratricyclo-[5.2.1.0<sub>2,6</sub>]dec-2-yl)methyl)pyridine, **23** (0.11 g, 0.375 mmol), as a light-brown viscous oil in 98% yield. <sup>1</sup>H NMR,  $\delta$  (ppm): 0.47 (q,  $J = 8.1$  Hz,  $J = 7.9$  Hz,  $J = 7.5$  Hz, 2H), 0.72 (t,  $J_1 = 7.6$  Hz,  $J_2 = 7.9$  Hz, 3H), 0.89 (s, 3H), 1.0 (s, 3H), 1.09 (s, 3H), 1.35 - 1.56 (m, 2H), 1.73 - 1.84 (m, 1H), 1.95 (d,  $J = 5.2$  Hz, 1H), 3.11 (dd,  $J_1 = 13.6$  Hz,  $J_2 = 13.6$  Hz, 2H), 4.28 (s, 1H), 7.15 (t,  $J_1 = 7.2$  Hz,  $J_2 = 5.4$  Hz, 1H), 7.23 (d,  $J = 7.8$  Hz, 1H), 7.59 (t,  $J_1 = 7.6$  Hz,  $J_2 = 6.1$  Hz, 1H), 8.5 (d,  $J = 4.8$  Hz, 1H). <sup>13</sup>C NMR,  $\delta$  (ppm): 7.4, 9.8, 20.8, 23.8, 24.1, 29.7, 42.3, 48.4, 48.9, 51.3, 87.5, 92.1, 121.5, 125.7, 128.4, 135.9, 148.3, 158.3.

**(1*S*,4*R*)-4,7,7-Trimethyl-3-pyridin-2-ylmethylenebicyclo[2.2.1]heptan-2-one, 24.**

To a solution of (1*S*,3*S*,4*R*)-3-hydroxy-4,7,7-trimethyl-3-pyridin-2-ylmethylenebicyclo[2.2.1]-heptan-2-one, **6** (0.10 g, 0.39 mmol) in toluene (1.0 mL) in a 25 mL two-neck round-bottom flask was added 1 M triethyl borane (0.39 mL, 0.39 mmol) and the solution was refluxed for 24 hours. The solvent evaporated from the reaction mixture leaving behind as a black solid, (1*S*,4*R*)-4,7,7-trimethyl-3-pyridin-2-ylmethylenebicyclo[2.2.1]heptan-2-one, **24** (0.073 g, 0.301 mmol., 77% yield). <sup>1</sup>H NMR,  $\delta$  (ppm): 0.92 (s, 3H), 0.98 (s, 3H), 1.20 (s, 3H), 1.40 - 1.61 (m, 2H), 1.88 - 2.04 (m, 2H), 2.30 (d,  $J = 4.42$  Hz, 1H), 6.61 (s, 1H), 7.18 (t,  $J_1 = 6.5$  Hz,  $J_2 = 5.0$  Hz, 1H), 7.70 (ddd,  $J_1 = 1.8$  Hz,  $J_2 = 1.7$  Hz,  $J_3 = 1.7$  Hz, 1H), 8.45 (d,  $J = 8.1$  Hz, 1H), 8.58 (d,  $J = 4.1$  Hz, 1H); <sup>13</sup>C NMR,  $\delta$  (ppm): 12.7, 17.7, 20.4, 22.3, 34.3, 45.8, 53.4, 60.3, 122.9, 125.4, 131.0, 136.2, 148.1, 148.7, 153.4, 205.6.

**(1*R*,2*R*,4*S*,4*a'**R*)-1'-ethyl-1,7,7-trimethylhexahydro-1'H-spiro[bicyclo[2.2.1]-heptane-2,3'-pyrido[1,2-c][1,3,2]oxazaborinin]-3-one, 25.**

To a solution of (1*S*,3*S*,4*R*,2'*R*)-3-hydroxy-4,7,7-trimethyl-3-piperidin-2'-ylmethylenebicyclo-[2.2.1]heptan-2-one, **16** (0.027 g, 0.103 mmol) in toluene (1.0 mL) in a 25 mL two-neck round-bottom flask was added 1 M triethyl borane (0.1 mL, 0.103 mmol) and the solution was then refluxed for 24 hours. Excess solvent was evaporated to afford (1*R*,2*R*,4*S*,4*a'**R*)-1'-ethyl-1,7,7-trimethylhexahydro-1'H-spiro[bicyclo[2.2.1]-heptane-2,3'-pyrido[1,2-c][1,3,2]oxazaborinin]-3-one, **25** (0.029 g, 0.098 mmol), as a dark-brown viscous oil in 95% yield. <sup>1</sup>H NMR,  $\delta$  (ppm): 0.75 (q,  $J_1 = 7.3$  Hz,  $J_2 = 8.0$  Hz,  $J_3 = 3.6$  Hz, 2H), 0.91 (s, 3H), 0.95 (t,  $J_1 = 7.4$  Hz,  $J_2 = 7.8$  Hz, 3H), 0.96 (s, 3H), 1.0 - 1.08 (m, 2H), 1.13 (s, 3H), 1.22 - 1.42 (m, 4H), 1.44 - 1.59 (m, 2H), 1.66 - 1.67 (m, 1H), 1.78 (m, 1H), 2.12 (d,  $J = 4.4$  Hz, 1H), 2.47 (dd,  $J_1 = 7.1$  Hz,  $J_2 = 7.1$  Hz, 2H), 2.68 - 2.77 (m, 1H), 2.85 - 2.94 (m, 1H), 3.18 (d,  $J = 12.1$  Hz, 1H). <sup>13</sup>C NMR,  $\delta$  (ppm): 7.4, 10.3, 20.6, 20.7, 21.9, 24.7, 24.8, 25.7, 30.4, 34.0, 40.9, 44.2, 50.7, 52.6, 62.6, 99.2, 109.3, 224.3.

**Typical procedure for the synthesis of 1-phenyl-1-propanol.**

To a solution of ligand (0.188 mmol) in dry toluene (3.6 mL) under argon in a 25 mL round-bottom flask at 0°C was added diethyl zinc (4.7 mmol). The reaction mixture was stirred for 1 hour at room temperature and then brought back to 0°C. Aldehyde (0.94 mmol) was then added dropwise with stirring and the reaction was allowed to proceed for 24 hours at 0°C. The reaction mixture was

treated afterward with 3 M HCl (15.0 mL), extracted with ethyl acetate (3 × 15 mL), rinsed with water (10.0 mL), backwashed with NaHCO<sub>3</sub> (5.0 mL), washed with brine and dried over magnesium sulfate and the solvent was removed under reduced pressure to afford slightly yellowish oil. This was purified by flash chromatography to afford pure 1-phenyl-1-propanol as a colorless liquid. R<sub>f</sub> 0.5 (hexane:ethyl acetate/2:1). <sup>1</sup>H and <sup>13</sup>C NMR spectra correlate with those reported earlier.<sup>6</sup> The purified product was analyzed by HPLC (Chiralcel OD or AD, hex./IPA 95:5, 0.7 mL/min., 254 nm).

## 5. Conclusions

We have described syntheses and structural characterization (including four X-ray crystal structures) of six new camphor-based amino alcohols and diols. These compounds were utilized as ligands for enantioselective additions of Et<sub>2</sub>Zn to benzaldehydes to obtain 1-phenylethanols. The highest enantioselectivity (77%) was obtained in the case of *p*-chlorobenzaldehyde with **13** as a ligand. The results show that amino 2,3-diol **7** (Table 3, entry 11) gave better asymmetric induction than the related 3-dehydroxy derivative [31] [32] **18a** (Table 3, entry 1) even at lower ligand concentration (Table 3, entry 12). The same did not work in the case of **18b** [32]. Adding a hydroxyl group at C3 of **18b** (*i.e.* converting **18b** to **13**) gave rise to a decrease of the catalytic performance. This together with the known better performance [25] of ligand **28** suggest that further studies aiming on better enantioselectivities through intelligent functionalization of these scaffolds should focus on derivatives of **27** and **28** instead of related 1,3-aminoalcohols (such as **18**), or hybrid compounds (*e.g.* **7** and **13**).

An attempt was also made in using amino diols **7** and **13** as ligands for enantioselective additions of terminal alkynes to aldehydes. Unfortunately the results were very poor. Our studies on these new ligands continue.

## Acknowledgements

We are grateful to the Chemistry and Biochemistry Department of the University of Massachusetts, Dartmouth for their financial support. We sincerely acknowledge University of Massachusetts Amherst for MS/HRMS measurements.

## References

- [1] Pu, L. and Yu, H.-B. (2001) Catalytic Asymmetric Organozinc Additions to Carbonyl Compounds. *Chemical Reviews*, **101**, 757-824. <https://doi.org/10.1021/cr000411y>
- [2] Lait, S.M., Rankic, D.A. and Keay, B.A. (2007) 1,3-Aminoalcohols and Their Derivatives in Asymmetric Organic Synthesis. *Chemical Reviews*, **107**, 767-796. <https://doi.org/10.1021/cr050065q>
- [3] Oguni, N. and Omi, T. (1984) Enantioselective Addition of Diethylzinc to Benzaldehyde Catalyzed by a Small Amount of Chiral 2-amino-1-alcohols. *Tetrahedron Letters*, **25**, 2823-2824. [https://doi.org/10.1016/S0040-4039\(01\)81300-9](https://doi.org/10.1016/S0040-4039(01)81300-9)
- [4] Salgado, A., Dejaegher, Y., Verniest, G., Boeykens, M., Gauthier, C., Lopin, C., Te-

- hrani, K.A. and De Kimpe, N. (2003) Synthesis of 1-alkyl-2-methylazetididin-3-ones and 1-alkyl-2-methylazetididin-3-ols. *Tetrahedron*, **59**, 2231-2239. [https://doi.org/10.1016/S0040-4020\(03\)00241-2](https://doi.org/10.1016/S0040-4020(03)00241-2)
- [5] Nugent, W.A. (2002) An Amino Alcohol Ligand for Highly Enantioselective Addition of Organozinc Reagents to Aldehydes: Serendipity Rules. *Organic Letters*, **4**, 2133-2136. <https://doi.org/10.1021/ol0259488>
- [6] Fontserat, M., Verdaguer, X., Sola, L., Vidal-Ferran, A., Reddy, K.S., Riera, A. and Pericas, M.A. (2002) Addition of Diethylzinc to Dicobalt Hexacarbonyl Complexes of  $\alpha,\beta$ -Acetylenic Aldehydes with Virtually Complete Enantioselectivity. A Formal Synthesis of (+)-Incrustoporin. *Organic Letters*, **4**, 2381-2833. <https://doi.org/10.1021/ol0260268>
- [7] Da, C.-S., Han, Z.-J., Ni, M., Yang, F., Liu, D.-X., Zhou, Y.-F. and Wang, R. (2003) A Convenient Synthesis of Piperidine-Based  $\beta$ -Amino Alcohols from l-Phe and Highly Enantioselective Addition of Diethyl Zinc to Aldehydes. *Tetrahedron: Asymmetry*, **14**, 659-665. [https://doi.org/10.1016/S0957-4166\(03\)00122-8](https://doi.org/10.1016/S0957-4166(03)00122-8)
- [8] Yus, M., Ramon, D.J. and Prieto, O. (2003) Synthesis of New C<sub>2</sub>-Symmetrical Bis-(hydroxycamphorsulfonamide) Ligands and Their Application in the Enantioselective Addition of Dialkylzinc Reagents to Aldehydes and Ketones. *Tetrahedron: Asymmetry*, **14**, 1103-1114. [https://doi.org/10.1016/S0957-4166\(03\)00045-4](https://doi.org/10.1016/S0957-4166(03)00045-4)
- [9] Kasashima, N., Hanyu, T., Aoki, T., Mino, M., Sakamoto, T. and Fujita, Y. (2005) Enantioselective Addition of Diethylzinc to Aldehydes Using Novel Chiral 1,4-aminoalcohols as Chiral Catalysts. *Journal of Oleo Science*, **54**, 495-504. <https://doi.org/10.5650/jos.54.495>
- [10] Jimeno, C., Vidal-Ferran, A. and Pericas, M.A. (2006) Ligand Anatomy: Probing Remote Substituent Effects in Asymmetric Catalysis through NMR and Kinetic Analysis. *Organic Letters*, **8**, 3895-3898. <https://doi.org/10.1021/ol0612197>
- [11] Huang, J., Ianni, J.C., Antoline, J.E., Hsung, R.P. and Kozlowski, M.C. (2006) De Novo Chiral Amino Alcohols in Catalyzing Asymmetric Additions to Aryl Aldehydes. *Organic Letters*, **8**, 1565-1568. <https://doi.org/10.1021/ol0600640>
- [12] Rodriguez-Escrich, S., Reddy, K.S., Jimeno, C., Colet, G., Rodriguez-Escrich, C., Sola, L., Vidal-Ferran, A. and Pericas, M.A. (2008) Structural Optimization of Enantiopure 2-Cyclialkylamino-2-aryl-1,1-diphenylethanol as Catalytic Ligands for Enantioselective Additions to Aldehydes. *The Journal of Organic Chemistry*, **73**, 5340-5353. <https://doi.org/10.1021/jo800615d>
- [13] Trost, B.M., Ngai, M.-Y. and Dong, G. (2011) Ligand-Accelerated Enantioselective Propargylation of Aldehydes via Allenylzinc Reagents. *Organic Letters*, **13**, 1900-1903. <https://doi.org/10.1021/ol200043n>
- [14] Yin, J., Huffman, M.A., Conrad, K.M. and Armstrong, J.D. (2006) Highly Diastereoselective Catalytic Meerwein-Ponndorf-Verley Reductions. *The Journal of Organic Chemistry*, **71**, 840-843. <https://doi.org/10.1021/jo052121t>
- [15] Lu, J., Xu, X., Wang, C., He, J., Hu, Y. and Hu, H. (2002) Synthesis of Chiral Ligands Derived from the Betti Base and Their Use in the Enantioselective Addition of Diethylzinc to Aromatic Aldehydes. *Tetrahedron Letters*, **43**, 8367-8369. [https://doi.org/10.1016/S0040-4039\(02\)01985-8](https://doi.org/10.1016/S0040-4039(02)01985-8)
- [16] Hanyu, N., Mino, T., Sakamoto, M. and Fujita, T. (2000) Facile Synthesis of Amino Bicyclo[2.2.1]heptyl Alcohol and Its Application for Enantioselective Additions of Diethylzinc to Aldehydes. *Tetrahedron Letters*, **41**, 4587-4590. [https://doi.org/10.1016/S0040-4039\(00\)00637-7](https://doi.org/10.1016/S0040-4039(00)00637-7)
- [17] Tanyeli, C., Odabaş, S., Erdem, M., Çakir, E. and Keskin, E. (2007) Asymmetric

- Synthesis of Novel 1,4-aminoalcohol Ligands with Norbornene and Norbornane Backbone: Use in the Asymmetric Diethylzinc Addition to Benzaldehyde. *Tetrahedron: Asymmetry*, **18**, 2349-2357. <https://doi.org/10.1016/j.tetasy.2007.09.019>
- [18] Olsson, C., Helgesson, S. and Frejd, T. (2008) New Bicyclic  $\gamma$ - and  $\delta$ -aminoalcohols as Catalysts for the Asymmetric Diethylzinc Addition to Benzaldehyde. *Tetrahedron: Asymmetry*, **19**, 1484-1493. <https://doi.org/10.1016/j.tetasy.2008.06.002>
- [19] Chai, Z., Liu, X.-Y., Zhang, J.-K. and Zhao, G. (2007) Enantioselective Addition of Alkenylzinc Reagents to Aldehydes with Organoboronates as the Alkenyl Source. *Tetrahedron: Asymmetry*, **18**, 724-728. <https://doi.org/10.1016/j.tetasy.2007.02.026>
- [20] Gilani, M. and Wilhelm, R. (2008) New Enantiopure Imidazolium Carbene Ligands Incorporating Two Hydroxy Groups for Lewis Acid-Catalyzed Diethyl Zinc Addition to Aldehydes. *Tetrahedron: Asymmetry*, **19**, 2346-2352. <https://doi.org/10.1016/j.tetasy.2008.10.011>
- [21] Niu, J.-L., Wang, M.-C., Lu, L.-J., Ding, G.-L., Lu, H.-J., Chen, Q.-T. and Song, M.-P. (2009) Enantioselective Addition of Alkynylzinc to Arylaldehydes Catalyzed by Azetidino Amino Alcohols Bearing an Additional Stereogenic Center. *Tetrahedron: Asymmetry*, **20**, 2616-262. <https://doi.org/10.1016/j.tetasy.2009.10.031>
- [22] Dean, M.A. and Hitchcock, S.R. (2010) Synthesis and Application of Oxadiazines as Chiral Ligands for the Enantioselective Addition of Diethylzinc to Aldehydes. *Tetrahedron: Asymmetry*, **21**, 2471-2478. <https://doi.org/10.1016/j.tetasy.2010.09.010>
- [23] Rachwalski, M., Lesniak, S. and Kielbasinski, P. (2010) Highly Enantioselective Addition of Phenylethynylzinc to Aldehydes Using Aziridine-Functionalized Tridentate Sulfinyl Ligands. *Tetrahedron: Asymmetry*, **21**, 2687-2689. <https://doi.org/10.1016/j.tetasy.2010.10.013>
- [24] Yoshida, K., Akashi, N. and Yanagisawa, A. (2011) Asymmetric Addition of Diethylzinc to Aldehydes Catalyzed by New Zinc-Amides Prepared by a Rhodium-Catalyzed Asymmetric Addition. *Tetrahedron: Asymmetry*, **22**, 1225-1230. <https://doi.org/10.1016/j.tetasy.2011.06.031>
- [25] Nevalainen, M. and Nevalainen, V. (2001) (+)-Camphor-Derived Amino Alcohols as Ligands for the Catalytic Enantioselective Addition of Diethylzinc to Benzaldehydes. *Tetrahedron: Asymmetry*, **12**, 1771-1777. [https://doi.org/10.1016/S0957-4166\(01\)00295-6](https://doi.org/10.1016/S0957-4166(01)00295-6)
- [26] Xu, P.-F., Chen, Y.-S. and Lu, T.-J. (2002) Chiral Tricyclic Iminolactone Derived from (1R)-(+)-Camphor as a Glycine Equivalent for the Asymmetric Synthesis of  $\alpha$ -Amino Acids. *The Journal of Organic Chemistry*, **67**, 2309-2314. <https://doi.org/10.1021/jo011139a>
- [27] Herzog, H. and Scharf, H.-D. (1986) An Improved Synthesis of (-)-(1R, 2S, 3R, 4S)-2-Benzyloxy-3-bornanol (12) on a Preparative Scale. *Synthesis*, **1986**, 788-790.
- [28] Olubanwo, O.B. (2010) Novel Camphor-Based Amino Alcohols and Diols for Selected Asymmetric Synthesis. Ph.D. Dissertation, University of Massachusetts, Lowell.
- [29] Calculations Were Conducted Using the MM2 Force-Field in Chem3D Ultra 8.0 Software CS, ChemOffice Chem3D Ultra 8.0, CambridgeSoft, Cambridge.
- [30] Smith, M.B. (2004) Organic Synthesis. McGraw-Hill, Boston, Chapter 4, 375, 388-392.
- [31] Xu, Q.Y., Wu, T.X. and Pan, X.F. (2001) Asymmetric Addition of Diethylzinc to Aldehydes Catalyzed by Chiral  $\gamma$ -Amino Alcohols. *Chinese Chemical Letters*, **12**, 1055-1056.

- [32] Le Goanvic, D., Holler, M. and Pale, P. (2002) Chiral Tridentate versus Bidentate Pyridines as Catalysts in the Enantioselective Alkylation of Benzaldehyde with Diethylzinc. *Tetrahedron: Asymmetry*, **13**, 119-121. [https://doi.org/10.1016/S0957-4166\(02\)00067-8](https://doi.org/10.1016/S0957-4166(02)00067-8)
- [33] Lygo, B., Crosby, J., Lowdon, T.R. and Wainwright, P.G. (2001) Structure-Selectivity Studies on Catalysts for the Phase-Transfer Catalysed Asymmetric Alkylation of Glycine Imine Esters. *Tetrahedron*, **57**, 2391-2402. [https://doi.org/10.1016/S0040-4020\(01\)00093-X](https://doi.org/10.1016/S0040-4020(01)00093-X)
- [34] Herdemann, M., Al-Mourabit, A., Martin, M.-T. and Marazano, C.J. (2002) From a Biogenetic Scenario to a Synthesis of the ABC Ring of Manzamine A. *Organic Chemistry*, **67**, 1890-1897. <https://doi.org/10.1021/jo0162033>
- [35] Grierson, D.S., Harris, M. and Husson, H.-P. (1980) Synthesis and Chemistry of 5,6-dihydropyridinium Salt Adducts. Synthons for General Electrophilic and Nucleophilic Substitution of the Piperidine Ring System. *Journal of the American Chemical Society*, **102**, 1064-1082. <https://doi.org/10.1021/ja00523a026>
- [36] Goldfuss, B. and Houk, K.N. (1998) Origin of Enantioselectivities in Chiral  $\beta$ -Amino Alcohol Catalyzed Asymmetric Additions of Organozinc Reagents to Benzaldehyde: PM3 Transition State Modeling. *The Journal of Organic Chemistry*, **63**, 8998. <https://doi.org/10.1021/jo9813787>
- [37] Goldfuss, B., Steigelmann, M., Khan, S.I. and Houk, K.N. (2000) Rationalization of Enantioselectivities in Dialkylzinc Additions to Benzaldehyde Catalyzed by Fenchone Derivatives. *The Journal of Organic Chemistry*, **65**, 77. <https://doi.org/10.1021/jo991070v>
- [38] Kitamura, M., Oka, H. and Noyori, R. (1999) Asymmetric Addition of Dialkylzincs to Benzaldehyde Derivatives Catalyzed by Chiral  $\beta$ -Amino Alcohols. Evidence for the Monomeric Alkylzinc Aminoalkoxide as Catalyst. *Tetrahedron*, **55**, 3605-3614. [https://doi.org/10.1016/S0040-4020\(98\)01167-3](https://doi.org/10.1016/S0040-4020(98)01167-3)
- [39] Scarpi, D., Galbo, F.L., Occhiato, E.G. and Guarna, A. (2004) Enantioselective Addition of Diethylzinc to Aldehydes Using 1,4-Aminoalcohols as Chiral Ligands. *Tetrahedron: Asymmetry*, **15**, 1319-1324. <https://doi.org/10.1016/j.tetasy.2004.03.004>
- [40] Lachance, H., St-Onge, M. and Hall, D.G. (2005) Practical and Efficient Multigram Preparation of a Camphor-Derived Diol for the Enantioselective Lewis Acid Catalyzed Allylboration of Aldehydes. *The Journal of Organic Chemistry*, **70**, 4180-4183. <https://doi.org/10.1021/jo050207g>