Boranes in synthesis — VII. Synthesis of 2-dialkylamino-6,6-dimethylbicyclo[3.1.1]heptan-3-ols from (R)-(+)-nopinone. Chiral auxiliaries for the addition of diethylzinc to aromatic aldehydes [†]

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Abstract: The reaction of (1R,5S)-(+)-nopinone with secondary amines in cyclohexane with the azeoptropic removal of water afforded excellent yields of the corresponding enamines. Hydroboration of these enamines with BMS followed by methanolysis and oxidation with basic hydrogen peroxide gave the corresponding (1R,2S,3S,5R)-2-dialkylamino-6,6-dimethylbicyclo[3.1.1]heptan-3-ols. These amino alcohols, in spite of their *trans* geometry, served as chiral auxiliaries for the addition of diethylzinc to aromatic aldehydes to give nearly quantitative yields of the corresponding (R)-1-aryl-1-propanols with 52 to 80% ee. © 1997 Published by Elsevier Science Ltd. All rights reserved.

β-Amino alcohols, especially those containing one or more stereogenic centers, are important in medicinal chemistry[1] and as chiral auxiliaries for a wide variety of asymmetric organic reactions,[2] more specifically, the enantioselective addition of organozinc reagents to aldehydes.[3] Recently, chiral auxiliaries derived from α-pinene have been used for a variety of asymmetric transformations, such as hydroboration and allylboration.[4] However, amino alcohols derived from pinene have seldom been used as chiral directors in organometallic reactions. Consequently, we were interested in synthesizing pinene-based amino alcohols. This paper describes the preparation of (1R,2S,3S,5R)-2-dialkylamino-6,6-dimethylbicyclo[3.1.1]heptan-3-ols 3a–d via the hydroboration/oxidation[5] of the corresponding enamines 2a–d of the chiral ketone (1R,5S)-(+)-nopinone[6] 1, and the use of 3a–d as chiral auxiliaries for the addition of diethylzinc to aromatic aldehydes.[7]

The reaction of 1 with secondary amines in refluxing cyclohexane[8] afforded excellent yields of the corresponding enamines 2 (Eq. 1). Hydroboration of 2 with BMS in THF followed by methanolysis and oxidation with basic hydrogen peroxide afforded moderate to good yields of the β-amino alcohols 3a–d (Eq. 2). In several cases, the reduced enamines 4 were significant or, as in the case of the pyrrolidine compound 2b, the major product of the hydroboration reaction.[9]

[†] Dedicated to Professor Herbert C. Brown on the occasion of his 85th birthday.
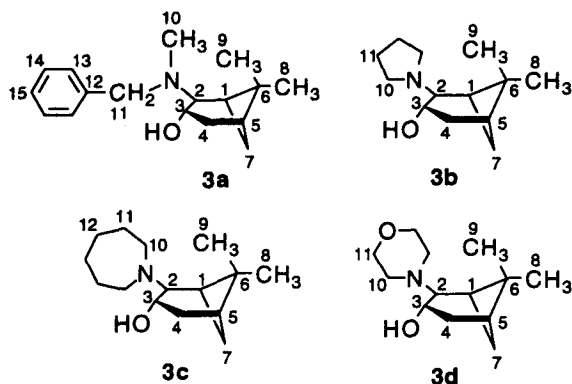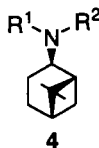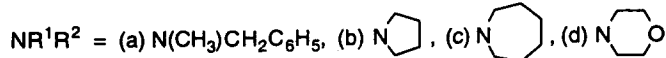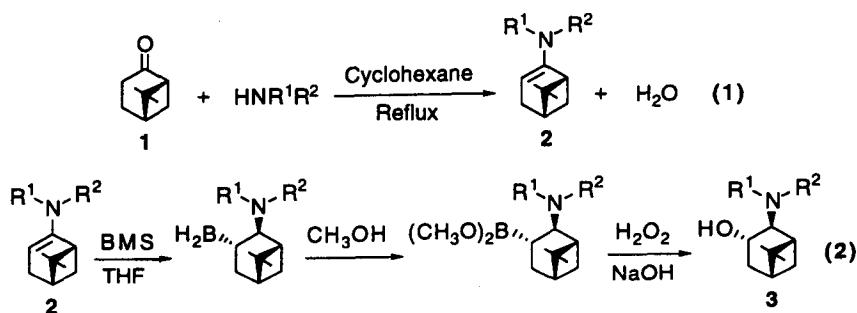[*] Corresponding author. Email: ctgoralski@dow.com

Figure 1. (1*R*,2*S*,3*S*,5*R*)-2-Dialkylamino-6,6-dimethylbicyclo[3.1.1]heptan-3-ols **3a–d**.

$$NR^1R^2 = \text{(a) } N(CH_3)CH_2C_6H_5, \text{ (b) } N\bigcirc, \text{ (c) } N\bigcirc, \text{ (d) } N\bigcirc O$$

NMR analysis

The structures of the β-amino alcohols **3a–d** (Figure 1) were confirmed by detailed analyses of their ^1H and ^{13}C NMR spectra, and the data are summarized in Table 1. The analysis of the spectra of **3c** served as an example. The ^1H NMR spectrum was assigned with the use of the 2D heteronuclear ^{13}C–^1H shift correlation experiment. The protons geminal to the nitrogen, H2, and the hydroxyl group, H3, are located at 2.77 and 4.16 ppm, respectively. The non-equivalent protons of carbon 4, H4 and H4*, were detected at 1.72 and 2.58 ppm. The couplings among these protons were used to assign the stereochemistry.

MM2 calculations have indicated that in the lowest energy conformation of 3-pinanylborane (3-bicyclo[3.1.1]heptanylborane; monoisopinocampheylborane, IpcBH₂) carbons 1 through 5 are coplanar.[10] This geometry leads to either eclipsed arrangements or dihedral angles of 120° for 3-bond couplings for the protons of carbons 2, 3, and 4. The Karplus equation predicts a value for the coupling constant for a given dihedral angle.[11] When the dihedral angle is 0° (eclipsed) the coupling is approximately 11 Hz while at 120° the coupling is predicted to be approximately 6 Hz. If electronegative groups are attached, as is the case for **3c**, a reduction in the magnitude of the coupling

Table 1. NMR (CDCl$_3$) data for (1R,2S,3S,5R)-2-dialkylamino-6,6-dimethylbicyclo[3.1.1]heptan-3-ols, **3a–d**[a]

position	compound 3a ^{1}H	^{13}C	compound 3b ^{1}H	^{13}C	compound 3c ^{1}H	^{13}C	compound 3d ^{1}H	^{13}C
1	2.43[b]	42.7	2.22[c]	44.5	2.33[d]	43.0	2.29[e]	41.4
2	2.64[f]	77.1	2.43[g]	78.3	2.77[h]	76.6	2.45[i]	77.3
3	4.29[j]	70.0	4.25[k]	69.9	4.16[l]	70.0	4.14[m]	69.3
4,4*	1.77, 2.66[n]	38.6	1.74, 2.57[o]	38.3	1.72, 2.58[p]	38.3	1.73, 2.64[q]	38.7
5	1.99[r]	41.1	1.94	41.4	1.93[s]	41.2	1.94	41.0
6	-----	36.6	-----	36.9	-----	36.7	-----	36.5
7,7*	1.19, 2.39[t]	29.6	1.11, 2.32[u]	29.9	1.14, 2.31[v]	29.8	1.16, 2.33[w]	29.2
8	1.26	27.0	1.23	27.2	1.23	27.2	1.22	26.9
9	1.12	22.8	0.99	22.8	1.02	22.8	0.98	22.7
10	2.10	39.7	2.50	52.7	2.67	52.8	2.44, 2.59	51.9
11	3.46, 3.77[x]	59.8	1.76	23.3	1.65	29.8	3.36	67.3
12	-----	140.5			1.55	27.1		
13	~7.45	128.4[y]						
14	~7.45	128.2[y]						
15	7.24	126.6						

[a]All chemical shift values are reported in δ ppm. The absolute values of the coupling constants are reported in Hz ± 0.2 Hz. An * designates the downfield proton of a nonequivalent methylene group. [b]$J_{1,2}$ = 2.9; $J_{1,7}$ ≅ 0. [c]$J_{1,2}$ = 2.9; $J_{1,7}$ ≅ 0. [d]$J_{1,2}$ = 2.8; $J_{1,5}$ = 5.0; $J_{1,7*}$ = 5.0; $J_{1,7}$ ≅ 0. [e]$J_{1,2}$ = 2.8. [f]$J_{2,3}$ = 3.1. [g]$J_{2,3}$ = 3.0. [h]$J_{2,3}$ = 2.8. [i]$J_{2,3}$ = 2.0. [j]$J_{3,4}$ = 3.2; $J_{3,4*}$ = 8.5. [k]$J_{3,4}$ = 3.0; $J_{3,4*}$ = 8.9. [l]$J_{3,4}$ = 3.0; $J_{3,4*}$ = 8.9. [m]$J_{3,4}$ = 3.0; $J_{3,4*}$ = 9.1. [n]$J_{4,4*}$ = 14.0; $J_{4,5}$ = 3.2; $J_{4*,5}$ = 2.4. [o]Couplings not determined. [p]$J_{4,4*}$ = 14.0; $J_{4,5}$ = 3.1; $J_{4*,5}$ = 2.3. [q]$J_{4,4*}$ = 14.0; $J_{4,5}$ = 3.0; $J_{4*,5}$ = 2.4. [r]$J_{5,7}$ ≅ 0. [s]$J_{5,7}$ ≅ 0; $J_{5,7*}$ = 5.0. [t]$J_{7,7*}$ = 9.2. [u]$J_{7,7*}$ = 9.9. [v]$J_{7,7*}$ = 9.2. [w]Not determined. [x]$J_{11,11*}$ = 13.6. [y]These assignments may be reversed.

occurs.[12] The observed couplings were $J_{2,3}$=2.8 Hz, $J_{3,4}$=3.0 Hz, and $J_{3,4*}$=8.9 Hz. These couplings were in qualitative agreement with the *trans*-orientation of the amino group and the hydroxyl group.

The relative stereochemistry of the hydroxyl group and the amino group, as well as the relationship between the hydroxyl group and the gem dimethyl methylene bridge, was established for compound **3c** by complexation with Eu(fod)$_3$ (Figure 2). The Eu(fod)$_3$ was intimately associated with the hydroxyl group. The protons on the same side of the ring as the hydroxyl group (H2, H3, and H4) were shifted downfield to a greater extent than the more distant protons. The methyl protons, H9, were slightly shifted downfield upon addition of Eu(fod)$_3$.

X-Ray structural analysis

The structure and conformation of **3a** was determined by single crystal X-ray analysis (Figure 3). Final cell parameters corresponded to a trigonal unit cell with a=14.488(3) Å, $b=a$, c=6.369(1) Å, and V=1157.8(8) Å^3. Acentric intensity statistics, and systematic absences of the form 00l, l=3n+1, identified the two isomorphic space groups as either P3$_1$ or P3$_2$. Structure solution using direct methods program SIR,[13] followed by successful refinement, indicated that space group P3$_1$ was the correct choice. Final refinement residuals after including hydrogen atoms in calculated positions were R=0.030, Rw=0.022, and S=1.17.

The structure contains a planar benzene ring. The nitrogen atom is close to tetrahedral, and the hydroxyl group is on the opposite side of the saturated six-membered ring from the dimethyl substituted bridging carbon. The molecules are held together in the crystal by a hydrogen bonding system, the shortest hydrogen bond being O· · ·H1–O with O· · ·H at 1.602 Å, and O· · ·O=2.689 Å. Surprisingly, there is no N (lone pair)· · ·H interaction up to 3.6 Å. Because the nitrogen has tetrahedral geometry (i.e., is not rehybridized) its lone pair must therefore be shielded by the bulk of the surrounding groups and thus is not available for hydrogen bonding interactions.
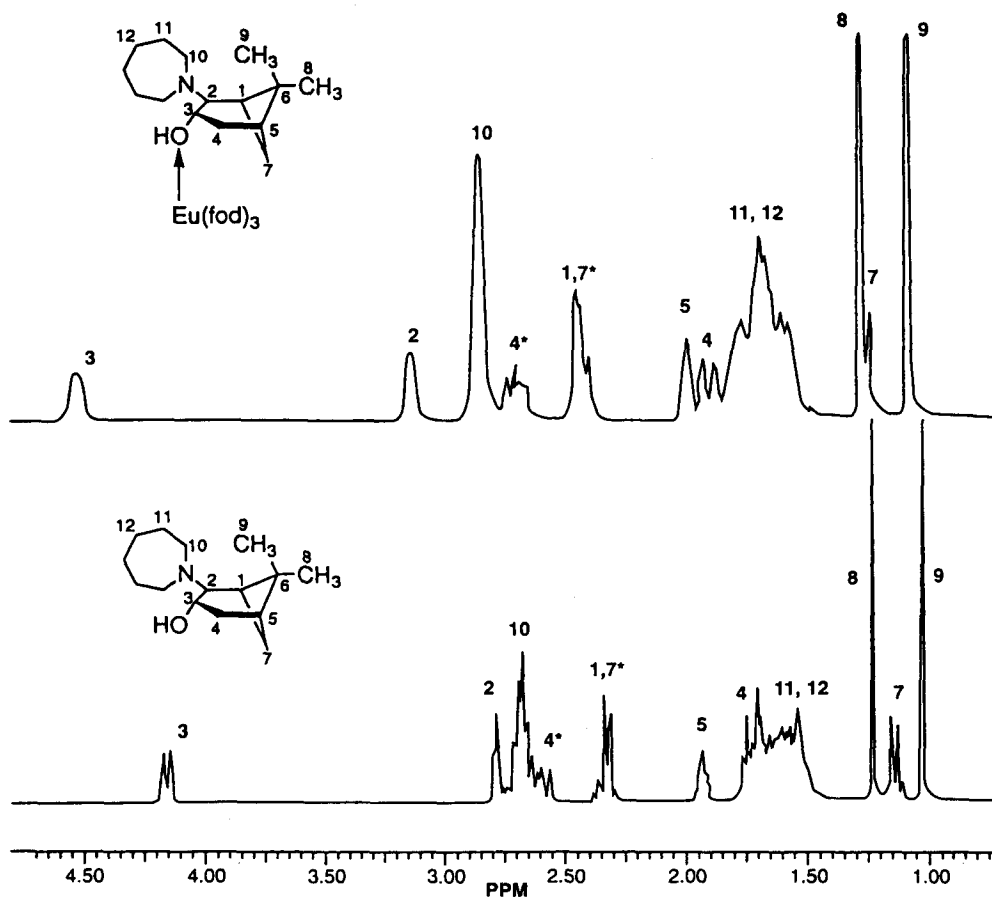
Figure 2. ¹H 300 MHz NMR spectrum (CDCl₃) of (1*R*,2*S*,3*S*,5*R*)-6,6-dimethyl-2-(1-hexamethyleneimino)bicyclo[3.1.1]-heptan-3-ol (**3c**) with and without added Eu(fod)₃.

Catalysis of the reaction of diethylzinc with aromatic aldehydes

The amino alcohols **3a–d** all reacted with *B*-methoxy-9-borabicyclo[3.3.1]nonane (*B*-methoxy-9-BBN) to form the corresponding non-chelated borinate esters **5a–d** (Eq. 3).

5a-d
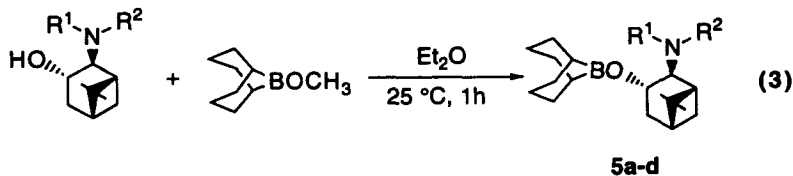
The esters all displayed a singlet at δ+56 in the ¹¹B NMR spectra. Since **5a–d** contain both a Lewis acid and a Lewis base in the same molecule, they were evaluated as catalysts for the asymmetric addition of diethylzinc to benzaldehyde. Unfortunately, diethylzinc reacted rapidly with these borinates to give *B*-ethyl-9-borabicyclo[3.3.1]nonane (Eq. 4).
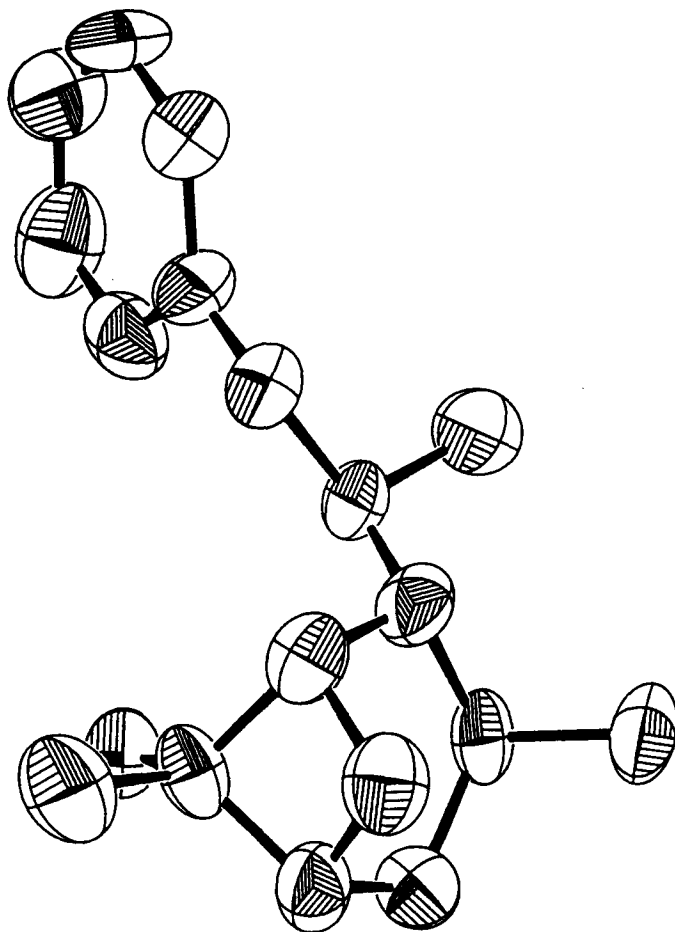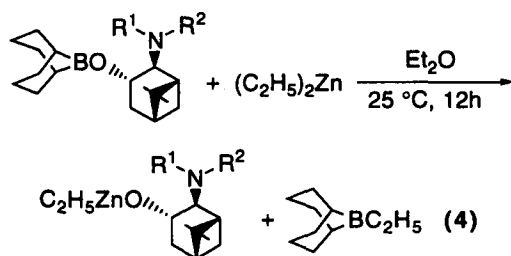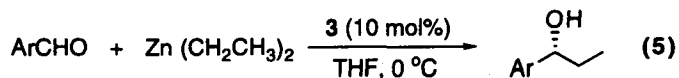
Figure 3. Molecular drawing of (1*R*,2*S*,3*S*,5*R*)-2-benzylmethylamino-6,6-dimethylbicyclo[3.1.1]heptan-3-ol (**3a**). The ORTEP thermal ellipsoids represent 50% probability.

Consequently, the amino alcohols **3a–d** were used as chiral auxiliaries for the addition of diethylzinc to benzaldehyde to give (*R*)-(+)-1-phenyl-1-propanol (Eq. 5, Ar=C_6H_5), and the results are summarized in Table 2.

Since **3a** gave the best results with benzaldehyde, it was selected as the catalyst to study the addition of diethylzinc to substituted benzaldehydes (Table 2).

Table 2. (R)-(+)-1-Aryl-1-propanols via the reaction of aromatic aldehydes with diethylzinc catalyzed by the amino alcohols **3a–d**

Ar	amino alcohol	ee, %[a,b]
C_6H_5	3a	80
C_6H_5	3b	76
C_6H_5	3c	70
C_6H_5	3d	63
4-ClC$_6$H$_4$	3a	75
4-CH$_3$C$_6$H$_4$	3a	73
4-CH$_3$OC$_6$H$_4$	3a	52

[a]Determined using HPLC and a Daicel brand CHIRALPAK AD stationary phase. [b]Corrected for the 92% optical purity of the starting (1R,5S)-(+)-nopinone.

Conclusions

Four (1R,2S,3S,5R)-2-dialkylamino-6,6-dimethylbicyclo[3.1.1]heptan-3-ols were obtained by hydroboration/methanolysis/oxidation of the corresponding enamines derived from (1R,5S)-(+)-nopinone. These were utilized as chiral auxiliaries and shown to be effective catalysts for the asymmetric addition of diethylzinc to aromatic aldehydes. The moderate to good asymmetric inductions realized in this study is significant because of the *trans* orientation of the hydroxyl and the tertiary amino groups, since most other catalysts of this nature can orient the hydroxyl and amino groups *cis* to one another.

Experimental section

General

All reactions were performed under nitrogen with glassware which had been previously dried at 140°C. The following procedures are typical, and all new compounds were completely characterized by IR, NMR, and elemental analyses. The single crystal X-ray data were collected at the Central Michigan University X-ray Diffraction Center. Measurements were made on a Rigaku AFC6S diffractometer with graphite monochromated MoKα radiation and a fine-focus sealed-tube X-ray source. Data were collected using CONTROL[14] software at ambient temperature, and analyzed using TEXAN.[15]

Morpholine enamine of (1R,5S)-(+)-nopinone 2d

A 100 mL, single neck flask equipped with a magnetic stirrer and a Dean–Stark trap fitted with a reflux condenser bearing a nitrogen bubbler was charged with 4.84 g (35 mmol) of (1R,5S)-(+)-nopinone (1), 50 mL of cyclohexane, and 11 mL of morpholine. The mixture was heated at reflux and the water collected. After seven days, the majority of the cyclohexane and the excess morpholine were distilled into the Dean–Stark trap. The residue was distilled at reduced pressure to give 6.64 g (91.5% yield) of **2d** as a colorless, viscous liquid, bp 76–78°C (0.4 Torr). Analysis Calcd for C$_{13}$H$_{21}$NO: N, 6.76. Found: N, 6.70.

Benzylmethylamine enamine of (1R,2S)-(+)-nopinone 2a

There was obtained from 5.52 g (40 mmol) of **1**, 6.04 g (62.5% yield) of **2a** as a pale yellow liquid, bp 130°C (0.4 Torr).

Pyrrolidine enamine of (1R,5S)-(+)-nopinone 2b

There was obtained from 4.92 g (35.6 mmol) of **1**, 5.39 g (79% yield) of **2b** as a pale yellow liquid, bp 83–85°C (0.6 Torr). Analysis Calcd for C$_{13}$H$_{21}$N: N, 7.32. Found: N, 7.10.

Hexamethyleneimine enamine of (1R,5S)-(+)-nopinone 2c

There was obtained from 4.83 g (35 mmol) of **1**, 6.91 g (90% yield) of **2c** as a pale yellow liquid, bp 100–103°C (0.9 Torr). Analysis Calcd for $C_{15}H_{25}N$: N, 6.38. Found: N, 6.48.

(1R,2S,3S,5R)-6,6-Dimethyl-2-(4-morpholino)bicyclo[3.1.1]heptan-3-ol 3d

The following procedure is representative: a 100 mL, single neck flask equipped with a magnetic stirrer and a Claisen adapter fitted with a nitrogen bubbler and a rubber septum was charged with 3.47 g (16.7 mmol) of **2d** and 10.5 mL of anhydrous THF. The resulting solution was cooled in an ice bath and 1.70 mL (17.0 mmol) of BMS (10 M) was added slowly. The reaction was stirred in the ice bath for 10 min., and then at room temperature for 2 h. The reaction mixture was treated with 4.0 mL of methanol and stirred at room temperature for 2 h. The reaction was mixed with 1.20 g (30 mmol) of solid sodium hydroxide, 2.5 mL of 30% hydrogen peroxide was added slowly, and the reaction was stirred at room temperature for 1 h. The organic layer was decanted away from a sticky, white solid which had formed. The solid was washed with three 30 mL portions of diethyl ether. The solvent was removed *in vacuo* from the combined organic layers leaving a clear oil. The oil was dissolved in 50 mL of methanol and the solution made acidic with concentrated HCl. The acidic solution was stirred at room temperature for 0.5 h. The methanol was removed *in vacuo* leaving a white, semi-solid. The solid was washed with two 30 mL portions of diethyl ether and vacuum dried to give 4.19 g. The solid was dissolved in 25 mL of water and the solution mixed with 30 mL of diethyl ether. The aqueous layer was made basic with 50% sodium hydroxide and the layers separated. The aqueous layer was extracted with five 30 mL portions of diethyl ether. The organic layers were combined and dried over anhydrous magnesium sulfate. The magnesium sulfate was separated by filtration and washed with two 30 mL portions of diethyl ether. The ether was removed *in vacuo* leaving 3.68 g (98% yield) of crude **3d** which rapidly crystallized. The crude **3d** was recrystallized from approximately 30 mL of hexane to give 2.65 g (71% yield) of **3d** as a white, crystalline solid, mp 84.5–86.5°C. $[\alpha]_D^{28}$=+21.1 (c=2.25, MeOH).[16] Analysis Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.28; H, 10.00; N, 6.14.

(1R,2S,3S,5R)-2-(Benzylmethylamino)-6,6-dimethylbicyclo[3.1.1]heptan-3-ol 3a

There was obtained 5.57 g (100% yield) of crude **3a**, as a white solid, from 5.16 g (41.4 mmol) of **2a**. The crude **3a** was analyzed by GC–MS and found to be a mixture of 20–25% **4a** and 75–80% **3a**, along with some other impurities. The crude **3a** was recrystallized from approximately 100 mL of hexane to give 1.82 g (33% yield) of **3a** as a white, crystalline solid, mp 134–136°C. $[\alpha]_D^{28}$=−2.8 (c=2.25, MeOH).[16] Analysis Calcd for $C_{17}H_{25}NO$: C, 78.71; H, 9.72; N, 5.40. Found: C, 78.27; H, 9.55; N, 5.33.

(1R,2S,3S,5R)-6,6-Dimethyl-2-(1-pyrrolidino)bicyclo[3.1.1]heptan-3-ol 3b

There was obtained 3.44 g (98% yield) of crude **3b**, as a pale yellow glass, from 3.19 g (16.7 mmol) of **2b**. The crude **3b** was distilled at reduced pressure to give 1.24 g of a colorless liquid, bp 90–100°C and 1.24 g of a colorless, viscous liquid, bp 107–110°C, which solidified. The solid was recrystallized from 10–15 mL of hexane to give 0.65 g (19% yield) of **3b** as a white solid, mp 67–69°C. $[\alpha]_D^{28}$=+31.3 (c=2.25, MeOH).[16] Analysis Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.28; H, 10.70; N, 6.58.

The first fraction was analyzed by GC–MS and found to be a mixture of 80% **4b** and 20% **3b**.

(1R,2S,3S,5R)-6,6-Dimethyl-2-(1-hexamethyleneimino)bicyclo[3.1.1]heptan-3-ol 3c

There was obtained 3.29 g (88% yield) of crude **3c**, as a colorless oil which rapidly crystallized, from 3.43 g (15.6 mmol) of **2c**. The solid was recrystallized from approximately 15 mL of hexane to give 0.82 g (22% yield) of **3c** as a white, crystalline solid, mp 96.5–97.5°C. $[\alpha]_D^{28}$=+45.6 (c=2.25, MeOH).[16] Analysis Calcd for $C_{15}H_{27}NO$: C, 75.89; H, 11.47; N, 5.90. Found: C, 75.76; H, 11.55; N, 5.97.

The solvent was removed *in vacuo* from the crystallization liquor leaving 2.24 g of pale yellow oil. This oil was analyzed by GC–MS and shown to be a mixture of 85% **4c** and 15% **3c**.

Reaction of diethylzinc with aromatic aldehydes catalyzed by amino alcohols 3a–d

The following procedure is representative: a 50 mL flask equipped with a magnetic stirring bar was charged with **3d** (0.23 g, 1.0 mmol). Diethylzinc in toluene (11.0 mL, ~12 mmol) was then introduced, with stirring, at 25°C. After 15 min, the reaction mixture was cooled to 0°C and benzaldehyde (1.0 mL, 10 mmol) was added with stirring. The reaction mixture was held at 0°C for 12 h. The reaction was then quenched with water (3 mL). After the initial exothermic reaction, 3 M hydrochloric acid (12 mL) was added and the reaction mixture was extracted with diethyl ether (3×5 mL). The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure (25°C, 12 Torr) and the crude (*R*)-(+)-1-phenyl-1-propanol was purified by distillation: bp 88–90°C (5 Torr); 1.3 g (>95% yield).

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16. These amino alcohols have a minimum enantiomeric excess (ee) of 92% based on the ee of the starting (*R*)-(+)-nopinone. It is entirely possible that during the recrystallization process the

enantiomeric excess was upgraded. This could not be accurately determined by HPLC analysis using a chiral stationary phase since a racemic mixture was not available to demonstrate the separation of the enantiomers.