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An efficient synthesis of enantiopure (+)- and (−)-*syn*-1,3-amino alcohols with a norbornane framework and their application in the asymmetric addition of $ZnEt_2$ to benzaldehyde

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Abstract—A series of new optically active (+)- and (−)-*syn*-1,3-amino alcohols with a norbornane framework has been synthesized. Their abilities as chiral catalysts in the enantioselective additions of $ZnEt_2$ to benzaldehyde were evaluated. High yields and enantiomeric excesses have been achieved (up to 91%). The influence of the configuration of the carbon bearing the hydroxyl group of the ligands has been studied. A plausible mechanism is also suggested for the observed enantioselectivity.

1. Introduction

1,3-Amino alcohols are important and versatile synthetic intermediates for many natural products[1] possessing potent biological activity such as nucleoside antibiotics[1a–d] or in alkaloids.[1e] They also possess relevance in the development of new enzyme inhibitors and the HIV protease inhibitor, ritonavir and lopinavir.[2] Consequently, these compounds became targets for the synthetic chemists, with different methodologies for their synthesis.[3]

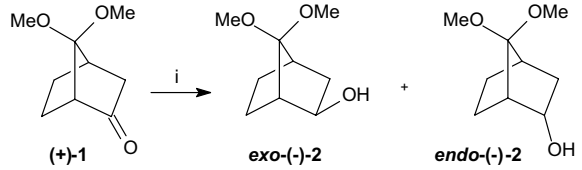
Since Noyori et al.[4] demonstrated the high efficiency of (−)-3-*exo*-(dimethylamino)isoborneol (DAIB) as a chiral catalyst for the addition of diethylzinc to benzaldehyde, many 1,2-amino alcohols have been prepared and applied as catalysts.[5] Until recently, only a few examples for the uses of 1,3-amino alcohols have been reported.[6] However, there has been increased interest in the application of 1,3-amino alcohols as chiral ligands for the catalyzed enantioselective addition of dialkylzinc to benzaldehyde,[7] although the reaction mechanism has been less studied.[7d–g]

In continuation of our work on the chemistry of enantiopure norbornane framework derivatives,[8] we herein report the synthesis of conformationally rigid enantiopure 1,3-amino alcohols and their evaluation as chiral ligands in the alkylation of benzaldehyde by diethylzinc.

2. Results and discussion

2.1. Synthesis of 1,3-amino alcohols

The reduction of ketone (+)-**1**, with known absolute configuration[9] and prepared by previously published procedures,[8] with $NaBH_4$ furnished a mixture of *endo*:*exo* (10:90) diastereomers. Separation of these isomers by flash chromatography rendered *exo*-(−)-**2** and *endo*-(−)-**2**-alcohols (also of known absolute configuration[9]) as pure isomers (Scheme 1). Alcohol *exo*-(−)-**2** was then treated with APTS to give ketoalcohol (+)-**3** (Scheme 2).



Scheme 1. Reagents and conditions: (i) $NaBH_4$, MeOH, rt, 2.5 h, 92%.

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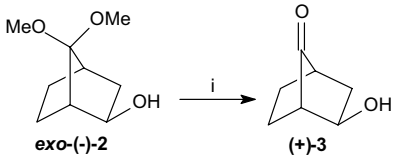
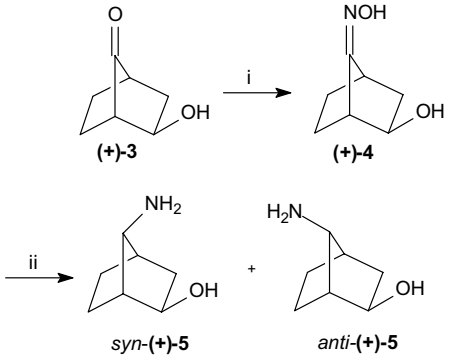


Scheme 2. Reagents and conditions: (i) APTS, acetone/water, rt, 5 h, 75%.

Treatment[10] of ketoalcohol (+)-**3** with $NH_2OH{\cdot}HCl$/NaOAc afforded hydroxy oxime (+)-**4**, while its reduction[11] with $NaBH_4/NiCl_2{\cdot}6H_2O$ at room temperature produced a mixture of *syn* and *anti* amino alcohols (Scheme 3).



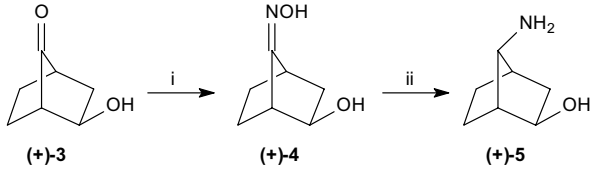
Scheme 3. Reagents and conditions: (i) $NH_2OH{\cdot}HCl$, NaOAc, MeOH, rt, 5 h; (ii) (a) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, MeOH, rt, 5 h.

In order to control the stereochemistry of this reaction, the temperature was varied as shown in Table 1. The best conditions to obtain the desired stereochemistry (100% *syn*) was achieved at −78 °C.

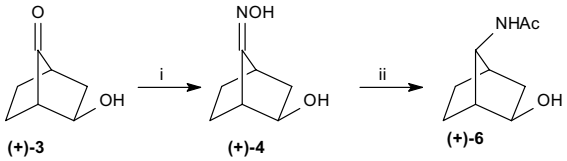
The direct solvent extractions of hydroxy oxime (+)-**4** or the respective amino alcohol (+)-**5** resulted in very poor yields. To overcome this, an in situ oximation with $NH_2OH{\cdot}HCl$/NaOAc followed by reduction with $NaBH_4/NiCl_2{\cdot}6H_2O$ was carried out producing a mixture with the respective amino alcohol (+)-**5**. At this stage, treatment of the mixture followed two ways: (a) $NaBH_4$ in formic acid to furnish amino alcohol (+)-**5** pure in 90% yield (Scheme 4), and (b) acetic anhydride producing acetamido alcohol (+)-**6** in 95% yield (Scheme 5). It is important to note that the amino alcohol racemic **5** has already been synthesized by Edwards et al.[12] from 2,3-iminonorbornane(3-azatricyclo[3.2.1.$0^{2,4}$]-octane), without isolating the pure product, which was characterized only as its *N*-benzoyl- and *N*-benzyloxycarbonyl derivatives.

Table 1. Effect of temperature in distribution of products under conditions of reductions

Temperature (°C)	*syn*:*anti*	Yield (%)
30	70:30	76
10	87:13	75
0	90:10	76
−78	100:0	90



Scheme 4. Reagents and conditions: (i) $NH_2OH{\cdot}HCl$, NaOAc, MeOH, rt, 5 h; (ii) (a) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, −78 °C, 10 h; (b) $NaBH_4$, HCO_2H, rt, overnight, 90%.



Scheme 5. Reagents and conditions: (i) $NH_2OH{\cdot}HCl$, NaOAc, MeOH, rt, 5 h; (ii) (a) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, −78 °C, 10 h; (b) Ac_2O, reflux, 5 h, 95%.

Acetamido alcohol (+)-**6** was reduced with $LiAlH_4$ to produce amino alcohol (+)-**7** with a yield of 91%. Amino alcohol (+)-**7** was treated with acetic anhydride to give acetamido ester (−)-**8**. The reduction of acetamido ester (−)-**8** with $LiAlH_4$ yielded diethylamino alcohol (+)-**9** in 73% yield. By using an Eschweiler–Clarke reaction[13] from (+)-**7**, *N*-methylethylamino alcohol (+)-**10** was synthesized (Scheme 6).

The synthesis of dimethylamino alcohol (+)-**11** was carried out by methylation of (+)-**5** with HCHO/HCOOH following the Eschweiler–Clarke reaction[13] (Scheme 7).

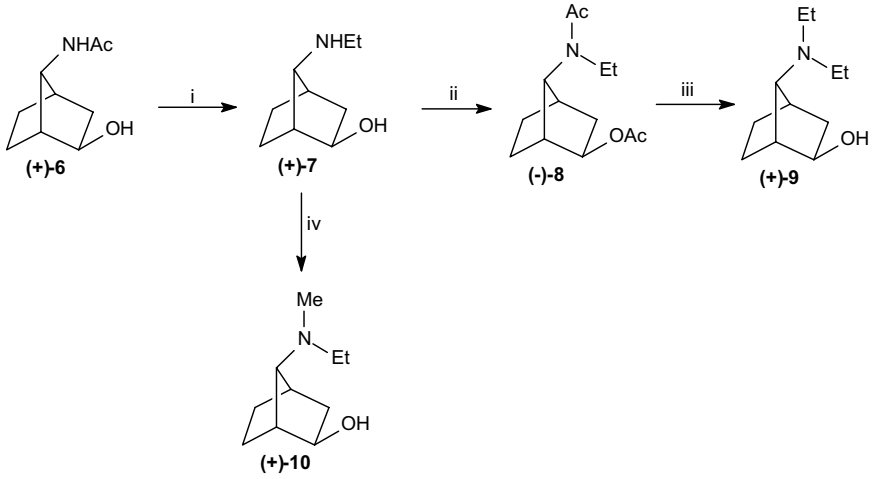
The description of this synthetic route is the same for the synthesis of the respective (−)-enantiomers (Scheme 8).

2.2. Enantioselective addition of diethylzinc to benzaldehyde

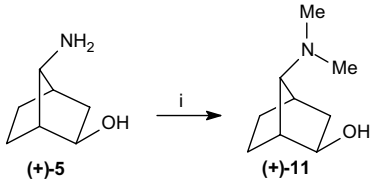
Acetamido alcohol **6** and amino alcohols **7**, **9**, **10** and **11** were evaluated as chiral auxiliaries to determine their ability to catalyze the enantioselective addition of diethylzinc to benzaldehyde (Scheme 9).

Initially the enantiomeric pairs of the 1,3-amino alcohols (−)-**9**, (+)-**9**, (−)-**11** and (+)-**11** were evaluated to determine the influence of the configuration of the carbon bearing the hydroxyl group. The addition reactions were carried out in toluene at room temperature in the presence of 8 mol% of these chiral ligands. The conditions used and the results obtained (entries 3, 4, 7 and 8) are summarized in Table 2.

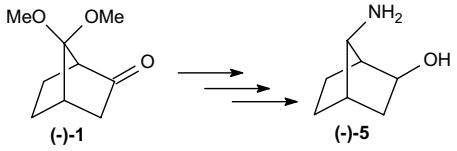
The catalysts afforded 1-phenylpropanol in high yields (90–94%) and good enantiomeric excesses (78–87%). In agreement with previous observations,[4d,5f,h] the absolute configuration of the 1-phenylpropanol correlates with the configuration of the hydroxyl-bearing stereocentre of the ligand. The (*R*)-1-phenylpropanol was obtained in 87% ee in the presence of (+)-**9** and (+)-**11**,



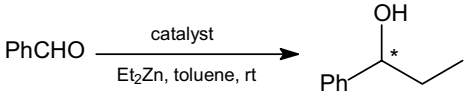
Scheme 6. Reagents and conditions: (i) $LiAlH_4$, THF, reflux, 4 h, 91%; (ii) AcO_2, reflux, 7 h, 95%; (iii) $LiAlH_4$, THF, reflux, 6 h, 73%; (iv) HCHO, HCOOH, reflux, 5 h, 73%.



Scheme 7. Reagents and conditions: (i) HCHO, HCOOH, reflux, 3 days 60%.



Scheme 8.



Scheme 9. Addition of diethylzinc to benzaldehyde.

respectively (Table 2, entries 3 and 8). The (*S*)-1-phenylpropanol was produced with (−)-**9** and (−)-**11** in 78% ee (Table 2, entries 4 and 7).

To study the effect of the catalyst's concentration, the enantiomers (−)-**9** and (+)-**11** were chosen. Comparing in Table 2, entries 4 and 8 with entries 5 and 9, it is possible to observe that the increase of the concentration from 8 to 20 mol% provokes a faster reaction time with excellent yields. The increase of the enantiomeric excesses was more significant for enantiomer (−)-**9**. Due to these observations, all the other reactions were performed with 20 mol% concentration.

Table 2. Addition of $ZnEt_2$ to benzaldehyde catalyzed by ligands (+)-**6**, (+)-**7**, (+)-**9**, (−)-**9**, (+)-**10**, (+)-**11** and (−)-**11**

Entry	Catalyst	Mol%	Time (h)[a]	Yield (%)[b]	Ee (%)[c]	Config.[c]
1	(+)-**6**	20	3	71	63	*R*
2	(+)-**7**	20	8	62	55	*R*
3	(+)-**9**	8	18	94	87	*R*
4	(−)-**9**	8	18	90	78	*S*
5	(−)-**9**	20	1	99	91	*S*
6	(+)-**10**	20	1	96	85	*R*
7	(−)-**11**	8	20	91	78	*S*
8	(+)-**11**	8	20	93	82	*R*
9	(+)-**11**	20	1	98	85	*R*

[a] The reaction was followed by GC.
[b] Determined by GC.
[c] Determined by chiral GC (Supelco β-Dex 120 30 m) 100 °C isothermal. 1-phenylpropanol: t_R (*R*) = 20.05 min, t_R (*S*) = 22.78 min.

The results show (Table 2) that overall moderate to excellent yields (62–99%) and enantioselectivities (55–91%) were obtained. *N*,*N*-Diethyl amino alcohol (−)-**9** (Table 2, entry 5) was found to be the most efficient of the series to catalyze the diethylzinc addition. However, the substituents on the nitrogen atom influence only slightly the selectivity of the transformation (Table 2, entries 5, 6 and 9). Nevertheless, when applying the *N*-ethylamino alcohol (+)-**7** and acetamido alcohol (+)-**6**, a decrease in the enantioselectivity and yield was obtained (Table 2, entries 1 and 2), due to the formation of the benzyl alcohol as byproduct. According to the literature,[4c,d] the acidic protons on the nitrogen may cause complications due to different chiral intermediates while parallel reaction pathways can be involved, thus complicating the induction.[5f]

2.3. Effect of conformation on facial selectivity

Several studies on the mechanism of the asymmetric organic additions to aldehydes catalyzed by amino alcohols have been reported.[4,14] These studies explain the

origin of the asymmetric induction, revealing the intermediates and the transition states involved in the reaction. The 5/4/4 tricyclic transition state described by Noyori and Yamakawa[4f,4h] explains the observed absolute configuration as well as the level of stereoselection in many of the cases. Panda et al.[7d] have carried out transition structure calculations to examine the reason for the selectivity for 1,3-amino alcohols and to verify, which of these ligands possess 6/4/4 tricyclic transition structures. In these cases, the Zn-atom is part of a more flexible six-membered ring in the catalytic chelate. A qualitative explanation of the results obtained for our 1,3-amino alcohols synthesized can be given by the 6/4/4 tricyclic transition structure.

The 1,3-amino alcohols initially react with diethylzinc liberating ethane. The resulting zinc ion then coordinates with the amine lone pair to form a six-membered ring (zinc aminoalkoxide **12**). The alkoxy oxygen atom **12** coordinates to diethylzinc to give the ethylzinc aminoalkoxide complex **13** (Fig. 1). Benzaldehyde coordinates to the face of complex **13** in two ways: *anti* (the two unreacting Et groups on the Zn atoms are *anti*) or *syn* (the two unreacting Et groups are *syn*). However, based on the Panda et al.[7d] studies, it is possible to define that the most stable transition state is *anti*.

As shown in Figure 2, in the transition states (*R*)-*anti*-**15** and (*S*)-*anti*-**17**, ethyl migrates to the *re*-face or *si*-face, respectively, of the benzaldehyde to form **16** and **18**. The transition model proposed in Figure 2 illustrates the (−)-1,3-amino alcohols attacking directly the *si*-face leading to the (*S*)-1-phenylpropanol, and the (+)-1,3-

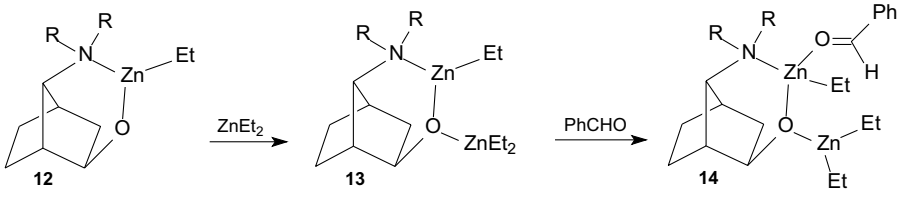


Figure 1.

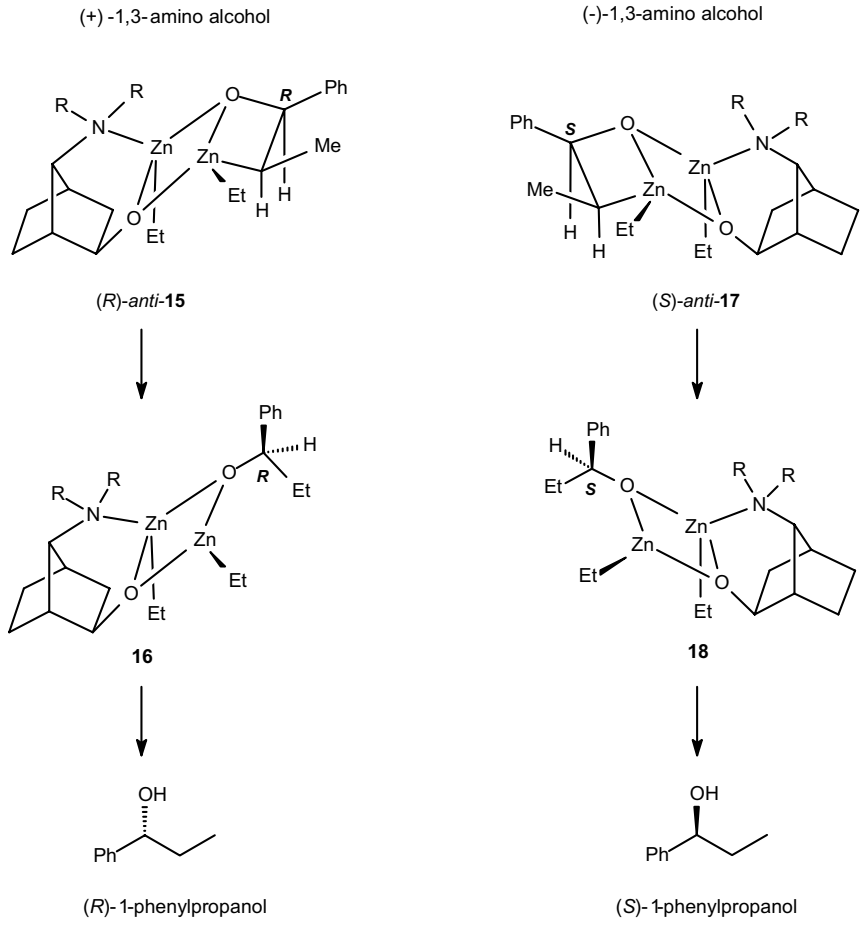


Figure 2. Facial selectivity of diethylzinc addition with (−) and (+)-1,3-amino alcohols.

amino alcohols attack directly to the *re*-face leading to the (*R*)-1-phenylpropanol.

3. Conclusions

A series of new optically active bicyclic *syn*-1,3-amino alcohols was synthesized with excellent yields. This route can be used to prepare various kinds of derivatives from these new ligands in enantiomerically pure forms. We have shown that homochiral *syn*-1,3-amino alcohols **9**, **10** and **11** are effective catalysts for the enantioselective addition of $ZnEt_2$ to benzaldehyde. The obtained results show clearly that the absolute configuration of the 1-phenylpropanol correlates with the configuration of the hydroxyl-bearing stereocentre of the ligand. The application of Noyori's mechanism to our system is a plausible model and can explain the facial selectivity observed in the reaction. These chiral ligands have conformationally rigid molecular structures and potential sites for metal coordinates. Therefore, they are very promising as potential chiral ligands for other asymmetric transformations.

4. Experimental

4.1. General

The reaction with $ZnEt_2$ requiring anhydrous conditions were conducted under an atmosphere of argon. Glassware, syringes and needles, for the transfer of the reagents, were dried at 180 °C and allowed to cool in a desiccator over $CaCl_2$ before use. THF and toluene were distilled from sodium and benzophenone under argon. Benzaldehyde was obtained from Aldrich and distilled prior to use. NMR spectra were obtained with a Varian YH-300 spectrometer in a magnetic field of 7.05 T in $CDCl_3$ or CD_3OD solution at 22 °C. A 5 mm multinuclear Varian probe was used. Chemical shifts are expressed in δ (ppm) relative to TMS as an internal standard and coupling constants (*J*) are given in hertz. Infrared spectra were recorded using a FTIR-Mattson 3020 spectrometer. Products were analyzed by GC on a Shimadzu chromatograph, model GC-17A a flame-ionization detector equipped with a column DB1 (15 m × 0.53 mm, 1.50 μm) and ee values determined by a Supelco β-Dex 120 chiral GC column (30 m × 0.25 mm (i.d.), 0.25 μm film column). Optical rotations were measured with a Perkin–Elmer polarimeter model 341 with a 1 cm cell at 20 °C. Melting points were determined on an Electrothermal IA 9100 digital melting point apparatus. HRMS spectra were obtained on a Mass Spectrometer Jeol AX500 (EB), EI (70 eV) or NICI with isobutane (200 eV).

The absolute configurations of all the compounds synthesized are proposed based on the previous determination of the absolute configurations of ketone (+)-**1** and of alcohol (−)-**2** by Lightner et al.[9]

The descriptions of the experimental procedures are the same for synthesis to the respective (−)- and (+)-products.

4.2. (−)-(1*S*,2*R*,4*R*)-7,7-Dimethoxynorbornan-2-*exo*-ol (−)-2

Ketone[8] (+)-**1** (1.09 g, 6.41 mmol) was dissolved in methanol (35 mL). The solution was cooled at 0 °C and, in small portions, powdered sodium borohydride (490 mg, 12.85 mmol) added under stirring. The solution was stirred at 0 °C for 3 h. The solvent was removed in a rotatory evaporator and water (20 mL) added to the residue. The solution was acidified with HCl 5% (pH 4) and extracted with Et_2O (3 × 60 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The residue, constituted as a 9:1 *exo*:*endo* mixture of diastereoisomers, was separated and purified by flash chromatography (silica, cyclohex/AcOEt 5.6:1 and 4:1). A clear oil was obtained (1.01 g, 5.90 mmol, 92%), which corresponded to compound (−)-**2** as a 9:1 *exo*:*endo* mixture of diastereoisomers.

exo-(−)-**2**: (silica, cyclohex/AcOEt 5.6:1), $[\alpha]_D^{20} = -30$ (*c* 1.36, AcOEt). FTIR (film): ν (cm^{-1}): 3539 (OH). ^1H NMR (300 MHz, $CDCl_3$): δ 1.10–1.13 (m, 2H), 1.61 (dm, $J = 13.6$ Hz, 1H), 1.70–1.77 (m, 2H), 1.86 (dd, $J = 13.6$ Hz, 8.0 Hz, 1H), 2.06 (d, $J = 4.3$ Hz, 1H), 2.15 (t, $J = 4.3$ Hz, 1H), 2.98 (s, OH), 3.28 (s, 3H), 3.31 (s, 3H), 3.72 (dd, $J = 8.0$ Hz, 2.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.4 (CH_2), 26.2 (CH_2), 37.7 (CH), 40.9 (CH_2), 44.2 (CH), 49.3 (OCH_3), 50.6 (OCH_3), 74.1 (CH), 114.7 (C). HRMS found: *m*/*z* 172.1080; calcd for $C_9H_{16}O_3$ $[M]^+$: 172.1099.

endo-(−)-**2**: (silica, cyclohex/AcOEt and 4:1), $[\alpha]_D^{20} = -1$ (*c* 3.07, AcOEt). FTIR (film): ν (cm^{-1}): 3409 (OH). ^1H NMR (200 MHz, $CDCl_3$): δ 0.98 (m, 1H), 1.88 (m, 2H), 2.12 (m, 3H), 3.05 (s, 3H), 3.09 (s, 3H), 4.3 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.5 (CH_2), 27.6 (CH_2), 38.4 (CH_2), 38.5 (CH), 43.8 (CH), 50.0 (CH_3), 50.5 (CH_3), 70.1 (CH), 114.1 (C).

4.3. (+)-(1*S*,2*R*,4*R*)-2-*exo*-Hydroxynorbornan-7-one (+)-3

To a solution of the alcohol *exo*-(−)-**2** (453 mg, 2.63 mmol) in acetone (9 mL) and water (1 mL), APTS (1.00 g, 5.27 mmol) was added. The mixture was stirred at room temperature for 5 h and then made alkaline with a saturated $NaHCO_3$ aqueous solution. The resulting suspension was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (silica, cyclohex/AcOEt 4:1) yielding 249 mg (1.98 mmol, 75%) of (+)-**3** as a colourless oil. $[\alpha]_D^{20} = +30$ (*c* 1.18, AcOEt). FTIR (film): ν (cm^{-1}): 3394 (OH), 1769 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 1.44–1.52 (m, 2H), 1.77–1.85 (m, 1H), 1.87–1.91 (m, 2H), 1.95 (d, $J = 4.2$ Hz, 1H), 2.08 (dd, $J = 13.4$ Hz, 8.1 Hz, 1H), 3.48 (s, OH), 4.07 (d, $J = 8.1$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.3 (CH_2), 22.7 (CH_2), 37.3 (CH_2), 37.8 (CH), 46.2 (CH), 69.4 (CH), 216.6 (C=O). HRMS found: *m*/*z* 126.0693; calcd for $C_7H_{10}O_2$ $[M]^+$: 126.0681.

4.4. (+)-(1*R*,2*R*,4*R*)-7-*syn*-Aminonorbornan-2-*exo*-ol (+)-5

To a stirred solution of the keto alcohol (+)-**3** (189 mg, 1.5 mmol) in methanol (27 mL) at room temperature, solid NaOAc (195 mg, 2.34 mmol) was added. The resulting mixture was stirred at room temperature until all the solid was dissolved. To the clear solution, solid $NH_2OH{\cdot}HCl$ (172 mg, 2.48 mmol) was added and the mixture was stirred at room temperature for 5 h. To this mixture nickel(II) chloride hexahydrate (627 mg, 2.64 mmol) was added and after complete dissolution, the solution was cooled to −78 °C. Powdered sodium borohydride (521 mg, 13.77 mmol) was added in small portions under efficient stirring. The stirring was continued for 12 h at −78 °C [at this point the mixture may be treated (in situ) according to Section 4.5 producing (+)-**6**, method (b)] and 85% formic acid (50 mL) and powdered sodium borohydride (1.35 g, 35.71 mmol) added. The mixture was stirred overnight at room temperature. The solvent was removed using a rotatory evaporator and the resulting mixture cooled to 0 °C, slowly quenched with 20% NaOH (20 mL) and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered and the solvent evaporated. The crude product was purified by chromatography (silica, $CHCl_3$/MeOH 4:1) giving 408 mg (3.21 mmol, 90%) of as yellow oil. $[\alpha]_D^{20} = +8$ (*c* 1.15, AcOEt). FTIR (film): *v* (cm^{-1}): 3360 and 3296 (NH_2, OH). ^1H NMR (300 MHz, $CDCl_3$): δ 0.96–1.15 (m, 2H), 1.43–1.68 (m, 2H), 1.82 (dd, *J* = 13.4 Hz, 7.1 Hz, 1H), 1.91–1.94 (m, 1H), 2.09–2.10 (m, 2H), 3.25 (b s, 4H; 1H, NH_2, OH), 3.72 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2 (CH_2), 27.1 (CH_2), 40.2 (CH_2), 40.9 (CH), 47.1 (CH), 60.5 (CH), 75.9 (CH). HRMS found: *m*/*z* 127.0975; calcd for $C_7H_{13}NO$ $[M]^+$: 127.0997.

(+)-(1*R*,2*R*,4*R*)-2-*exo*-Hydroxynorbornan-7-one oxime (+)-**4**: Mp = 143.6–144.6 °C. $[\alpha]_D^{20} = +41$ (*c* 1.01, MeOH). FTIR (KBr): *v* (cm^{-1}): 3306 (OH), 1707 (C=N). ^1H NMR (300 MHz, CD_3OD): δ 1.29–1.39 (m, 2H), 1.51–1.54 (m, 1H, *syn*), 1.55–1.57 (m, 1H, *anti*), 1.61–1.71 (m, 2H), 1.92 (dd, *J* = 11.4 Hz, 7.4 Hz, 1H), 2.27 (d, *J* = 4.7 Hz, 1H, *anti*), 2.40 (t, *J* = 4.7 Hz, 1H, *anti*), 3.05 (d, *J* = 4.1 Hz, 1H, *syn*), 3.10 (t, *J* = 4.1 Hz, 1H, *syn*), 3.89 (dd, *J* = 7.4 Hz, 2.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.3 (CH_2, *syn*), 23.5 (CH_2, *anti*), 26.7 (CH_2, *anti*), 27.8 (CH_2, *syn*), 32.7 (CH, *anti*), 37.4 (CH, *syn*), 40.6 (CH_2, *anti*), 40.9 (CH_2, *syn*), 41.3 (CH, *syn*), 45.8 (CH, *anti*), 73.1 (CH, *anti*), 73.4 (CH, *syn*), 168.4 (C=NOH). HRMS found: *m*/*z* 141.0810; calcd for $C_7H_{11}NO_2$ $[M]^+$: 141.0790.

4.5. (+)-(1*R*,2*R*,4*R*)-7-*syn*-Acetamidonorbornan-2-*exo*-ol (+)-6

The mixture containing amino alcohol (+)-**5** (190 mg, 1.5 mmol), obtained in Section 4.4, was treated in situ with acetic anhydride (11 mL) and refluxed for 5 h. The residue was neutralized with a solution of saturated potassium carbonate and extracted with Et_2O (3 × 30 mL), yielding, after solvent evaporation, a white solid corresponding to compound (+)-**6** (249 mg, 1.47 mmol, 95%). Mp = 78.4–80.1 °C. $[\alpha]_D^{20} = +63$ (*c* 1.17, AcOEt). FTIR (film): *v* (cm^{-1}): 3355 (OH, NH), 1649 (C=O), 1537 (C–N). ^1H NMR (300 MHz, $CDCl_3$): δ 0.98–1.12 (m, 2H), 1.57–1.71 (m, 3H), 1.83 (dd, *J* = 13.9 Hz, 7.3 Hz, 2H), 1.96 (s, 3H), 2.07–2.09 (m, 1H), 2.31 (b s, 1H), 3.51 (s, OH), 3.92–3.95 (m, 1H), 3.96–3.99 (m, 1H), 7.34 (b s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.9 (CH_2), 23.8 (CH_3), 26.6 (CH_2), 39.3 (CH_2), 40.1 (CH), 45.7 (CH), 58.8 (CH), 75.9 (CH), 170.5 (C=O). The molecular ion was too weak for an exact mass measurement, so the elemental composition was confirmed by data from its substrate (+)-**5** and its product (+)-**7**.

4.6. (+)-(1*R*,2*R*,4*R*)-7-*syn*-Ethylaminonorbornan-2-*exo*-ol (+)-7

In a 100 mL three-necked round-bottomed flask under argon, $LiAlH_4$ (172 mg, 4.53 mmol) was suspended in dry THF (10 mL). Compound (+)-**6** (253 mg, 1.51 mmol) in dry THF (15 mL) was added dropwise and the resulting mixture refluxed for 4.5 h. The solution was cooled to 0 °C, quenched slowly with 10% NaOH (20 mL) and diluted with $CHCl_3$ (40 mL). The resulting mixture was stirred overnight at room temperature, filtered, dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. Compound (+)-**7** was obtained as white solid (213 mg, 1.37 mmol, 91%). Mp = 42–43.7 °C. $[\alpha]_D^{20} = +17$ (*c* 1.45, AcOEt). FTIR (film): *v* (cm^{-1}): 3296 (OH, NH). ^1H NMR (300 MHz, $CDCl_3$): δ 0.80–1.10 (m, 2H), 1.06 (t, *J* = 7.1 Hz, 3H), 1.37–1.58 (m, 3H), 1.75–1.83 (m, 1H), 2.10–2.20 (m, 2H), 2.62 (q, *J* = 7.1 Hz, 2H), 2.88–2.92 (m, 1H), 3.19 (b s, OH, NH), 3.62–3.68 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.2 (CH_3), 22.9 (CH_2), 27.1 (CH_2), 39.1 (CH), 40.8 (CH_2), 42.8 (CH_2), 45.4 (CH), 67.7 (CH), 75.9 (CH). HRMS found: *m*/*z* 155.1303; calcd for $C_9H_{17}NO$ $[M]^+$: 155.1310.

4.7. (−)-(1*R*,2*R*,4*R*)-7-*syn*-(Acetylethyl)aminonorbornan-2-*exo*-yl acetate (−)-8

Compound (+)-**7** (160 mg, 1.03 mmol) was dissolved in acetic anhydride (24 mL) and refluxed for 6 h. The residue was neutralized with a solution of saturated potassium carbonate and extracted with Et_2O (3 × 30 mL). The organic layers were dried over $MgSO_4$. After filtration and evaporation, the crude product was purified by silica gel column chromatography using chloroform and methanol (99:1) as the eluent to give the corresponding compound (−)-**8** (234 mg, 1.28 mmol, 95%). $[\alpha]_D^{20} = -21$ (*c* 1.09, AcOEt). FTIR (film): *v* (cm^{-1}): 1726 (C=O), 1648 (C=O amide), 1421 (C–N). ^1H NMR (300 MHz, $CDCl_3$): δ 1.15 (t, *J* = 7.1 Hz, 3H), 1.11–1.25 (m, 2H), 1.58–1.69 (m, 1H), 1.71–1.80 (m, 2H), 1.91 (t, *J* = 7.6 Hz, 1H), 1.95 (s, 3H), 2.11 (s, 3H), 2.54–2.57 (m, 1H), 3.12 (s, 1H), 3.20–3.40 (m, 2H), 3.47 (b s, 1H), 4.69 (dd, *J* = 7.6 Hz, 2.93 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 20.9 (CH), 22.8 (CH_3), 23.2 (CH_2), 25.6 (CH_2), 37.7 (CH_2), 37.8 (CH), 41.8 (CH_2), 42.9 (CH_3), 63.4 (CH), 76.9 (CH), 170.4 (C=O), 172.5 (C=O). HRMS found: *m*/*z* 239.1517; calcd for $C_{13}H_{21}NO_3$ $[M]^+$: 239.1521.

4.8. (+)-(1*R*,2*R*,4*R*)-7-*syn*-Diethylaminonorbornan-2-*exo*-ol (+)-9

Following Section 4.6, 164 mg (0.658 mmol) of (−)-**8** were reduced with 150 mg (3.95 mmol) of $LiAlH_4$ in dry THF (15 mL). The mixture was refluxed for 6 h. After stirring, the solution was cooled to 0 °C, quenched slowly with 10% NaOH (10 mL) and diluted with $CHCl_3$ (30 mL). The resulting mixture was stirred overnight at room temperature, filtered, dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using chloroform and methanol (95:5) as an eluent to give the corresponding compound (+)-**9** (112 mg, 0.480 mmol, 73%). $[\alpha]_D^{20} = +5$ (*c* 1.04, AcOEt). FTIR (film): *v* (cm^{-1}): 3365 (OH). ^1H NMR (300 MHz, $CDCl_3$): δ 1.02 (t, $J = 7.3$ Hz, 3H), 0.99–1.10 (m, 2H), 1.48–1.57 (m, 2H), 1.82–1.84 (m, 2H), 2.31 (s, 1H), 2.35–2.37 (m, 1H), 2.70–2.71 (m, 1H), 2.76 (m, 2H), 3.70–3.73 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6 (CH_2), 27.1 (CH_2), 37.4 (CH), 40.7 (CH_2), 44.4 (CH), 70.9 (CH), 75.7 (CH). HRMS found: *m*/*z* 183.1639; calcd for $C_{11}H_{21}NO$ $[M]^+$: 183.1623.

4.9. (+)-(1*R*,2*R*,4*R*)-7-*syn*-Ethylmethylaminonorbornan-2-*exo*-ol (+)-10

To 200 mg (1.29 mmol) of (+)-**7**, 5 mL of formaldehyde (36% H_2O solution) and 9 mL of 85% formic acid were added. The solution was then refluxed for 5 h. The resulting mixture was cooled to 0 °C, made alkaline with 20% NaOH (pH = 10) and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered and the solvent evaporated. The crude product was purified by column chromatography (silica, $CHCl_3$/MeOH 99:1) yielding 159 mg (0.94 mmol, 73%) of as colourless oil. $[\alpha]_D^{20} = +12$ (*c* 1.13, AcOEt). FTIR (film): *v* (cm^{-1}): 3368 (OH). ^1H NMR (300 MHz, $CDCl_3$): δ 0.80–1.30 (m, 2H), 1.04 (t, $J = 7.2$ Hz, 3H), 1.44–1.58 (m, 2H), 1.60–1.78 (m, 3H), 1.82 (dd, $J = 13.4$ Hz, 6.8 Hz, 1H) 2.22 (s, 3H), 2.28–2.32 (m, 2H), 2.38 (s, 1H), 3.66 (d, $J = 6.8$ Hz, 1H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.5 (CH_3), 22.9 (CH_2), 26.8 (CH_2), 27.2 (CH_2), 37.5 (CH), 39.5 (CH_3), 40.7 (CH_2), 44.7 (CH), 74.5 (CH), 75.9 (CH). HRMS found: *m*/*z* 169.1459; calcd for $C_{10}H_{19}NO$ $[M]^+$: 169.1467.

4.10. (+)-(1*R*,2*R*,4*R*)-7-*syn*-Dimethylaminonorbornan-2-*exo*-ol (+)-11

To 300 mg (2.36 mmol) of (+)-**5**, 9 mL of formaldehyde (36% H_2O solution) and 17 mL of 85% formic acid were added and the solution refluxed for 3 days. The resulting mixture was cooled to 0 °C, made alkaline with 20% NaOH (pH = 10) and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered and the solvent evaporated. The crude product was purified by column chromatography (silica, $CHCl_3$/MeOH 5.6:1) giving 220 mg (1.42 mmol, 60%) of as yellow liquid. $[\alpha]_D^{20} = +22$ (*c* 1.08, AcOEt). FTIR (film): *v* (cm^{-1}): 3376 (OH). ^1H NMR (300 MHz, $CDCl_3$): δ 0.90–1.01 (m, 2H), 1.34–1.51 (m, 2H), 1.62–1.67 (m, 1H), 1.73 (dd, $J = 13.7$ Hz, 6.8 Hz, 1H) 2.11 (s, 1H), 2.16 (s, 6H), 2.20–2.22 (m, 2H), 3.57 (d, $J = 6.8$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.8 (CH_2), 27.1 (CH_2), 37.6 (CH), 40.3 (CH_2), 44.3 (CH_3), 44.5 (CH), 75.8 (CH), 76.2 (CH). HRMS found: *m*/*z* 155.1311; calcd for $C_9H_{17}NO$ $[M]^+$: 155.1310.

4.11. General procedure for the enantioselective alkylation of benzaldehyde with diethylzinc

To the catalyst (0.125 mmol), diethylzinc (2.0 mL, 2.0 mmol, 1 M in hexane) was slowly added. The resulting solution was stirred at room temperature for 1 h. Benzaldehyde (0.625 mmol, 0.066 g, 0.064 mL) was added dropwise causing the solution to acquire a yellow colour. The reaction mixture was stirred at rt and the progress of the reaction monitored by GC (the solution acquire a pale yellow colour). The reaction was quenched with aqueous HCl (10%, 8 mL) and extracted with diethyl ether (4×5 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give the crude reaction mixture, which was analyzed by GC. GC conditions (Supelco β-Dex 120, 30 m, 0.25 mm i.d.); isotherm at 100 °C. t_R: benzaldehyde 4.18 min, benzyl alcohol 14.51 min, (*R*)-(+)-1-phenylpropanol 22.05 min, (*S*)-(+)-1-phenylpropanol 22.78 min.

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