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Synthesis of chiral norbornane derivatives as γ-amino alcohol catalysts: the effect of the functional group positions on the chirality transfer

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Abstract—Starting from (1*S*,4*R*) chiral ketone (+)-**6**, we developed a synthetic route to the synthesis of new chiral γ-amino alcohols (+)- and (−)-*syn*-2-amino-7-hydroxy norbornane derivatives with excellent yields and enantiomeric excesses (up to 99%). These compounds were tested as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde presenting moderate results. The results obtained, compared with others previously reported, showed that the relative disposition of the amino and hydroxyl groups on C(2) and C(7) positions, play an important role in the catalytic activity.

1. Introduction

Chiral amino alcohols are very important compounds used in organic synthesis with several applications, such as chiral auxiliaries,[1] synthetic intermediates,[2] and chiral legends for asymmetric synthesis.[3] They also posses high biological activity, which is used in HIV protease inhibitors.[4]

Nucleophilic addition of organometallic reagents to carbonyl compounds is a very important operation in organic synthesis, and its asymmetric version is particularly useful.[5] Since the initial work of Oguni and Omi with (*S*)-leucinol,[6] followed by Noyori's work with **DAIB**,[7] the asymmetric addition of diethylzinc to aldehydes catalyzed by chiral amino alcohols has attracted considerable attention. The reaction is one of the most reliable reactions for testing the effectiveness of newly developed chiral ligands.[5,8] γ-Amino alcohols have been studied less than β-amino alcohols but have demonstrated satisfactory results.[9] In a recent work, we described the synthesis of new enantiopure γ-amino alcohols *syn*-2-hydroxy-7-amino norbornane derivatives with high yields and enantiomeric excesses (Fig. 1).[9c]

Their evaluation as chiral ligands in the enantioselective addition of diethylzinc to benzaldehyde was also described, presenting satisfactory results when the compound (+)-**3** was used (91% ee).[9c]

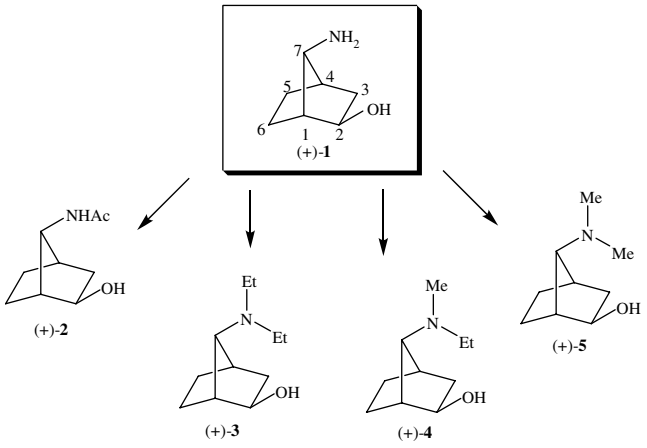

Figure 1. Synthesis of enantiopure γ-amino alcohols.

Inspired by these results, we decided to synthesize a new enantiopure norbornane derivative namely γ-amino alcohol 2-amino-7-hydroxy derivative (−)-**12**, which presents the functional groups in opposite positions when compared with compound (+)-**1**. Its evaluation as a chiral inductor in the enantioselective addition of diethylzinc to benzaldehyde is also described.

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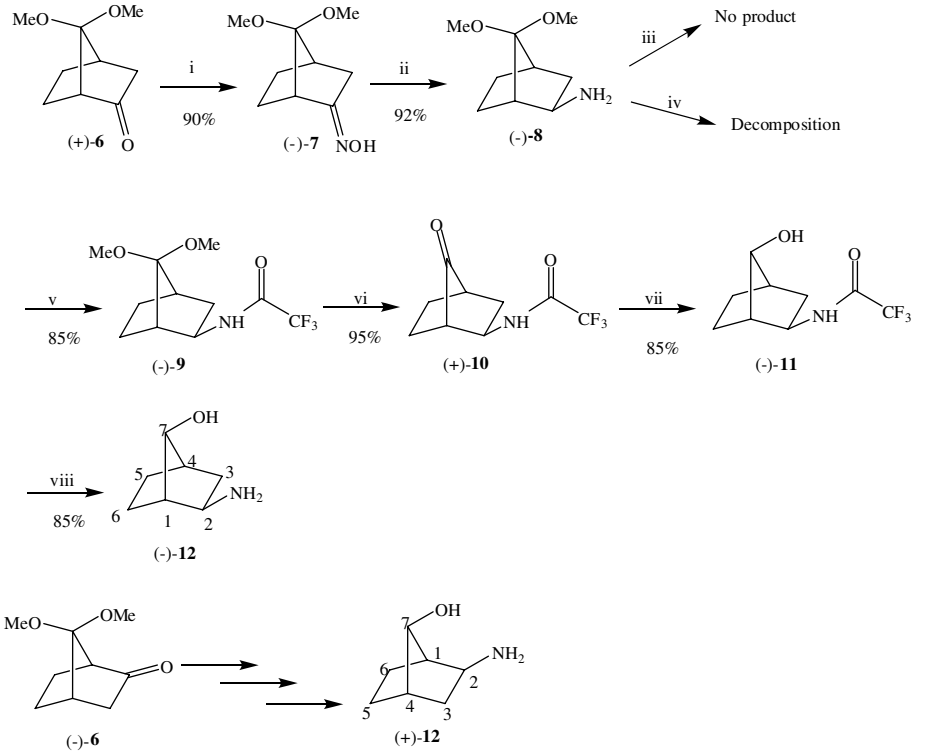
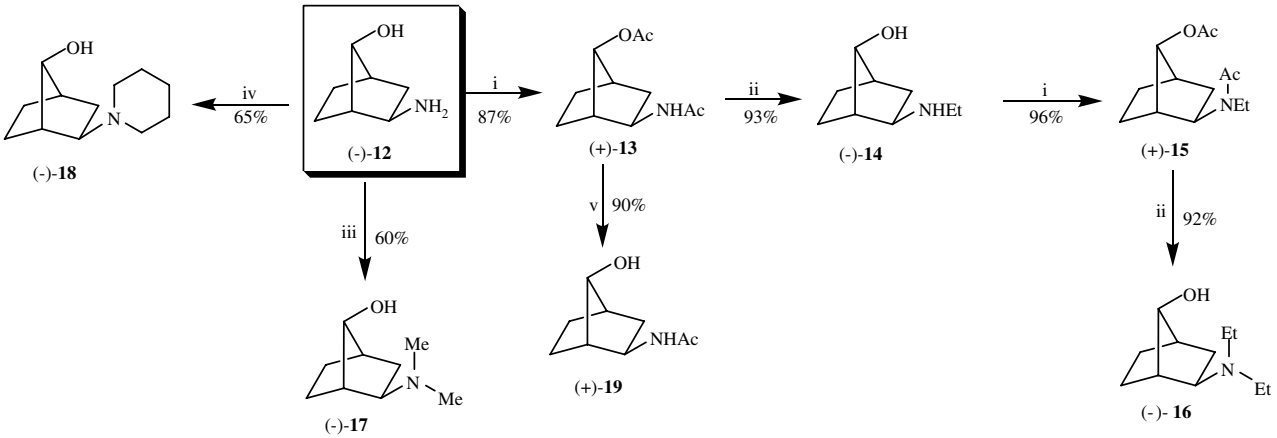
2. Results and discussion

Herein, compound (−)-**12** was obtained following Scheme 1. The oxime (−)-**7** was obtained by the treatment of (1*S*,4*R*) chiral ketone (+)-**6** (up to 99% ee)[9c,10c] with hydroxylamine chloridrate and sodium acetate. The reduction of (−)-**7** with $NaBH_4/NiCl_2{\cdot}6H_2O$, followed by treatment with formic acid, provided amine (−)-**8**.[9c] Attempts at removing the ketal group of (−)-**8** failed at room temperature. When the reaction was performed at reflux, decomposition occurred. To overcome this problem, we protected the amino group by the treatment of (−)-**8** with trifluoroacetic anhydride providing the trifluoroacetamide (−)-**9**.[11] Treatment of (−)-**9** with *p*-toluenesulfonic acid and acetone, at reflux, provided ketone (+)-**10**. *syn*-Alcohol (−)-**11** was obtained by reduction of (+)-**10** with L-Selectride and finally, the 1,3-*syn*-amino alcohol (−)-**12** obtained through the treatment of (−)-**11** with potassium carbonate in methanol.[12] The (+)-**12** enantiomer was synthesized from (−)-**6** by the same methodology with similar yields and enantiomeric excesses.

After the synthesis of chiral γ-amino alcohol (−)-**12**, we decided to synthesize its derivative (−)-**16**, which is an isomer of (+)-**3**[9c] (Fig. 1), together with other derivatives to



Scheme 1. Reagents and conditions: (i) $NH_2OH{\cdot}HCl$, NaOAc, CH_3OH, 15 h, rt; (ii) (a) $NaBH_4/NiCl_2{\cdot}6H_2O$, CH_3OH, 6 h, −78 °C, (b) $NaBH_4$, H_2CO_2; (iii) *p*-toluenesulfonic acid, acetone/H_2O, 24 h, rt; (iv) *p*-toluenesulfonic acid, acetone/H_2O, reflux; (v) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, 15 h, rt; (vi) *p*-toluenesulfonic acid, acetone, reflux, 2 h; (vii) L-Selectride, THF, −78 °C, 4 h; (viii) K_2CO_3, CH_3OH/H_2O, 2 h, reflux.



Scheme 2. Reagents and conditions: (i) $(CH_3CO)_2O$, reflux, 3 h; (ii) $LiAlH_4$, THF, reflux, 4 h; (iii) H_2CO_2, H_2CO, reflux, 7 days; (iv) 1,5-diiodopentane, K_2CO_3, CH_3OH/H_2O, reflux, 1 h; (v) HCl 20%, THF, 15 h.

study their abilities as chiral inductors (Scheme 2). The treatment of (−)-**12** with acetic anhydride provided compound (+)-**13**. Compound (−)-**14** was obtained by reduction of (+)-**13** with $LiAlH_4$. The acetylation reaction of (−)-**14**, furnished compound (+)-**15**. Finally the N,N-diethylated amino alcohol (−)-**16** was obtained by $LiAlH_4$ reduction.

On the other hand, treatment of (−)-**12** with formic acid and formaldehyde[9c] provided compound (−)-**17**. The piperidino derivative (−)-**18** was obtained by treatment of (−)-**12** with 1,5-diiodopentane and potassium carbonate.[13] The hydrolysis of compound (+)-**13** with 20% HCl provided hydroxy acetamide (+)-**19**.

2.1. Enantioselective addition of diethylzinc to benzaldehyde

Using chiral compounds **16**–**19** as catalysts, we have performed the enantioselective addition of diethylzinc to benzaldehyde. The addition reactions were carried out in toluene at room temperature in the presence of 20 or 40 mol % of these chiral ligands (Table 1).

The catalysts afforded 1-phenylpropanol in high yields (83–98%) and moderate enantiomeric excesses (30–78%). The absolute configuration of the major enantiomer of 1-phenylpropanol correlates with the configuration of the hydroxyl-bearing stereocenter (C–O). This was already observed by Vilar et al.[14] who reported that the stereochemical outcome is mainly controlled by the hydroxyl group with regards to its relative position in the norbornane skeleton.

The reaction with γ-amino alcohol catalysts seemed to be very sensitive to steric hindrance, as already observed by Aoyama.[9d] The best results were obtained with the enantiomeric pairs of the N,N-diethylated compounds, (+)- and (−)-**16**, and the piperidino derivatives (+)- and (−)-**18**. An increase in the amount of catalyst amount did not provide a significant change in the enantiomeric excess of the 1-phenylpropanol.

As shown in Table 1, compound **16** induced 68% enantiomeric excess in the 1-phenylpropanol in spite of the 91% ee obtained by its isomer (+)-**3**.[9c] However, the presence of a piperidinic ring caused a slight increase in the enantioselectivity, probably due to steric effects (Table 1, entries 6–8). Aoyama et al. observed the same enantiomeric excess (77% ee) obtained with an isoborneol γ-amino alcohol piperidino derivative.[9d]

2.2. Mechanism and facial selectivity

Figure 2 shows the transition state proposed for γ-amino alcohols,[9c,d,15] for the asymmetric reaction. Molecular orbital and density functional calculations indicate that the *anti* coordination of benzaldehyde (with respect to the chiral ligand) and a 6/4/4 tricyclic transition state are most favorable.[15]

Analysis of Figure 2 shows that, in the transition states *anti*-(2*R*,7*S*)- and *anti*-(2*S*,7*R*)-, the ethyl group migration occurs in the *si*-face and *re*-face, respectively, of benzaldehyde. The (2*R*,7*S*)-amino alcohol predominantly forms the (*S*)-1-phenylpropanol while the (2*S*,7*R*)-amino alcohol predominantly forms the (*R*)-1-phenylpropanol. In other words, the configuration of the 1-phenylpropanol correlated with the configuration of the hydroxyl-bearing stereocenter (C–O), which is in agreement with previous observations.[7d,9c,14]

It is well known that the stereo chemical outcome is mainly controlled by the hydroxyl group,[7d,9c,14] therefore, the C–O stereocenter position is a fundamental parameter in the 1-phenylpropanol enantiomeric excess. Figure 3 compares the results of the enantioselective addition of diethylzinc to benzaldehyde catalyzed by (+)-**1**[9c] and (−)-**12** derivatives.

The exchange in the C2 and C7 positions of the amino and hydroxyl functional groups leads to a significant decrease in the enantiomeric excess of 1-phenylpropanol. The results obtained show that the preferential position to the hydroxyl group is attached to C-2, which provides a higher enantioselectivity.

3. Conclusions

In this work, we have developed a synthetic route to the synthesis of new chiral γ-amino alcohols *syn*-2-amino-7-hydroxy norbornane derivatives with excellent yields and enantiomeric excesses (up to 99%). The compounds were evaluated as chiral inductors in the enantioselective addition of diethylzinc to benzaldehyde presenting moderate

Table 1. Enantioselective addition of diethylzinc to benzaldehyde catalyzed by 1,3-amino alcohols derived from (−)-**12**

Entry	Catalyst	Mol (%)	Time[a] (h)	Yield[b] (%)	ee[c] (%)	Config.[c]
1	(−)-**16**	20	15	84	68	*S*
2	(+)-**16**	20	15	83	68	*R*
3	(−)-**16**	40	15	98	67	*S*
4	(−)-**17**	20	18	85	44	*S*
5	(−)-**17**	40	18	89	40	*S*
6	(−)-**18**	20	19	92	78	*S*
7	(−)-**18**	40	20	93	76	*S*
8	(+)-**18**	20	20	90	77	*R*
9	(+)-**19**	20	19	95	30	*S*

[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*) = 30.48 min, t_R (*S*) = 31.99 min.

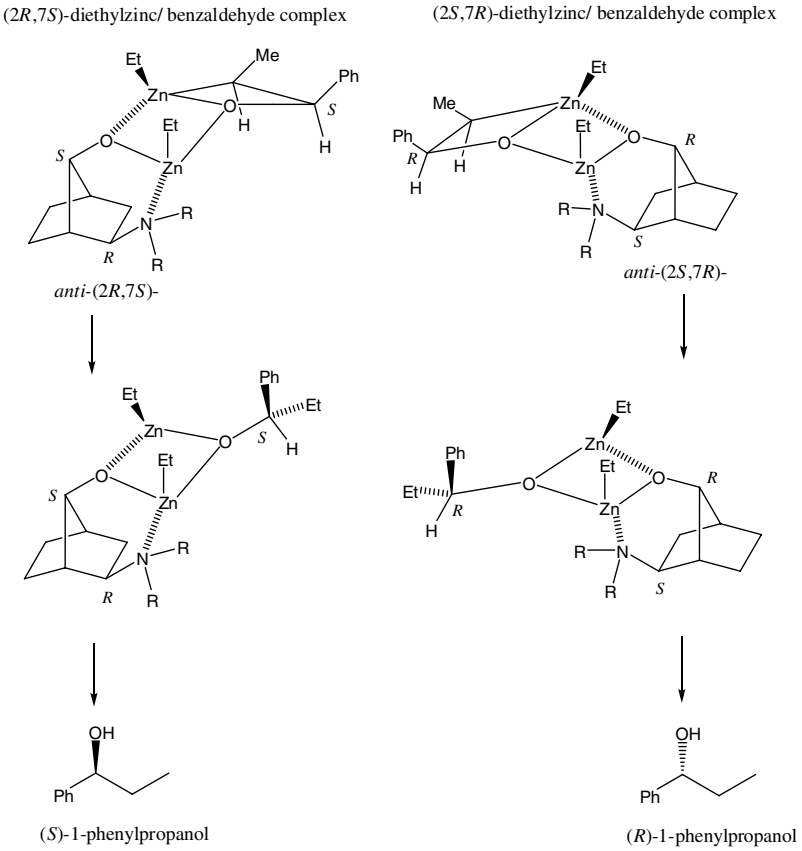


Figure 2. 6/4/4/Transition state and facial selectivity of the diethylzinc addition to benzaldehyde to γ-amino alcohols.

results. The results obtained clearly show that the absolute configuration of the 1-phenylpropanol correlates with the configuration of the hydroxyl-bearing stereocenter of the ligand, as observed in a previous work.[7d,9c,14] We also observed that the exchange in the C2 and C7 positions of the amino and hydroxyl functional groups of (+)-**1**[9c] derivatives, leading to (−)-**12** derivatives, led to a significant decrease in enantiomeric excess of 1-phenylpropanol. The presence of a piperidinic ring in the γ-amino alcohol structure (compound **18**) provided an increase in the enantioselectivity, probably, due to steric effects.

These chiral ligands have very rigid molecular structures and a favorable stereochemistry for metal coordination. Therefore, we believe that compounds (+)- and (−)-**12** are promising chiral ligand precursors, which may be used in other types of asymmetric transformations.

4. Experimental

4.1. General

Melting points were measured on a BUCHI B-545 melting point apparatus. NMR spectra were measured with a VARIAN VXR200 ($B_0 = 4.7$ T) and YH-300 ($B_0 = 7.05$ T). Chemical shifts are expressed as δ (ppm) relative to TMS as an internal standard and the J values are given in hertz. The products were analyzed by GC on a Shimadzu GC-17A gas chromatograph, equipped with a FID detector. Column DB1 (15 m × 0.53 mm) and ee values were determinated by a Supelco β-Dex 120 chiral GC column (30 m × 0.25 mm). Optical rotations were measured in a Perkin–Elmer 341 polarimeter with a 0.1 dm cell at a temperature of 20 °C. High resolution mass spectrometric analysis was obtained with a Jeol AX500 (EB), EI (70 eV) or NICI with isobutene (200 eV) mass spectrometer. Lipase AY Amano 30 (*Candida rugosa*), Lot. LAYY0405102S was kindly provided by Amano Enzyme USA Co. Ltd.

Lipase catalyzed transesterification was the source of chirality of the compound (+)-**6** precursors providing excellent enantiomeric excesses (up to 99%).[9c,10c,16]

The absolute configurations of all compounds synthesized were proposed based on the previous determination of the absolute configuration of ketone (+)-**6** by Lightner et al.[10a]

4.2. (−)-7,7-Dimethoxy-2-oximo-norbornane (−)-7

To a stirred solution of (+)-**6** (1.7 g, 10 mmol) in methanol (50 mL) were added $NH_2OH{\cdot}HCl$ (1.4 g, 20 mmol) and NaOAc (1.7 g, 20.7 mmol). The resulting mixture was stirred for 15 h at room temperature and then the methanol was evaporated. The resulting material was neutralized with a 10% $NaHCO_3$ solution and extracted with chloroform. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated providing 1.66 g (90%) of a light yellow solid. All spectral data confirm the structure of the chiral oxime (−)-**7**, however the melting point does

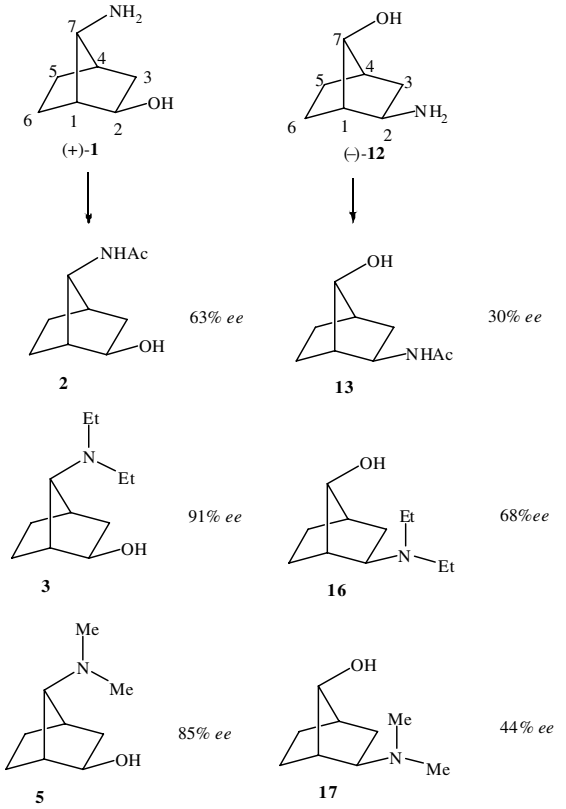


Figure 3. Results of the asymmetric addition of diethylzinc to benzaldehyde catalyzed by (+)-**1** and (−)-**12** derivatives.

not agree with that obtained by Marchand[17] even after several purifications. Mp: 109–112 °C (lit.[15] 89–92). $[\alpha]_D^{20} = -35.5$ (*c* 1.07, AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 1.45 (m, 2H), 1.95 (m, 2H), 2.41 (s, 1H), 2.65 (m, 2H), 2.85 (s, 1H), 3.25 (s, 3H), 3.28 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 25.1 (CH_2), 26.7 (CH_2), 33.5 (CH_2), 38.4 (CH), 45.3 (CH), 50.8 (CH_3), 51.6 (CH_3). FTIR ($CHCl_3$): γ (cm^{-1}) 3269 (OH), 1693 (C=N). HRMS found: *m*/*z* 185.1055; calcd for $C_9H_{15}NO_3$ [M^+]: 185.1082.

4.3. (−)-7,7-Dimethoxy-2-*exo*-amino-norbornane (−)-8

To a stirred solution of (−)-**7**, (1.8 g, 9.7 mmol) in methanol (50 mL) was added $NiCl_2$·6HCl (3.3 g, 19 mmol). The mixture was stirred until all the nickel chloride had dissolved after which it was cooled to −78 °C. $NaBH_4$ (3.3 g, 87 mmol) was added slowly and the mixture was stirred for 6 h in this temperature. After 6 h, formic acid was added (60 mL) followed by another amount of $NaBH_4$ (3.7 g, 97 mmol) very slowly. The mixture was stirred over night at room temperature and then evaporated. The crude material was neutralized with a 10% NaOH solution and extracted with Et_2O. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated providing 1.53 g (92%) of a yellow oil. $[\alpha]_D^{20} = -18.1$ (*c* 1.05, AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.28 (s, 3H), 3.26 (s, 4H), 2.13 (s, 1H), 1.92 (s, 1H), 1.785 (m, 2H), 1.25 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 24.8 (CH_2), 26.1 (CH_2), 38.0 (CH), 38.9 (CH_2), 44.8 (CH), 50.0 (CH), 50.4 (CH), 54.6 (CH), 114.2 (C). FTIR ($CHCl_3$): γ (cm^{-1}) 3385 (NH). The HRMS was not obtained because of rapid decomposition of the amine (−)-**8**, therefore the elemental composition was confirmed by data from its substrate (−)-**7** and its product (−)-**9**.

4.4. (−)-7,7-Dimethoxy-2-*exo*-trifluoroacetamide-norbornane (−)-9

To a cooled solution (0 °C) of (−)-**8** (1 g, 5.8 mmol) in CH_2Cl_2 (30 mL) were added 2 mL of trifluoroacetic anhydride (14.5 mmol) and 2 mL of Et_3N (14.5 mmol). The mixture was stirred for 15 h at room temperature and then washed with 20 mL of water. The organic layer was separated and dried over anhydrous $MgSO_4$, filtered, and evaporated providing 1.32 g (85%) of a yellow oil. $[\alpha]_D^{20} = -7.4$ (*c* 1.2, AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.10 (m, 1H), 3.30 (s, 3H), 3.29 (s, 3H), 2.5 (s, 1H), 2.19 (s, 1H), 2.01 (s, 2H), 1.85 (m, 2H), 1.33 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 24.0 (CH_2), 26.2 (CH_2), 37.2 (CH_2), 37.6 (CH), 43.0 (CH), 50.1 (CH), 50.7 (CH_3), 50.8 (CH_3), 115.9 (CF_3) (q, $J_{C-F} = 287.3$ Hz), 155.6 (C) (q, $J_{C-F} = 36.4$ Hz). FTIR ($CHCl_3$): γ (cm^{-1}) 3302 (NH), 1645 (C=O). HRMS found: *m*/*z* 267.1099; calcd for $C_{11}H_{16}NO_3F_3$ [M^+]: 267.1082.

4.5. (+)-2-*exo*-Trifluoroacetamide-7-one-norbornane (+)-10

To a solution of (−)-**9** (1.5 g, 5.6 mmol) in acetone (30 mL), *p*-toluenesulfonic acid was added (3.2 g, 16.8 mmol) and refluxed for 2 h. The mixture was evaporated and the crude product neutralized with a 10% $NaHCO_3$ solution. The mixture was extracted with chloroform, dried over anhydrous $MgSO_4$, filtered, and evaporated providing 1.5 g of a brown oil. The crude product was purified by flash chromatography (silica, cyclohexane/AcOEt 4:1) yielding 1.1 g (95%) of a brown solid. Mp: 127–129 °C. $[\alpha]_D^{20} = +8.5$ (*c* 2.0, AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.14 (m, 1H), 2.00 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 20.7 (CH_2), 22.6 (CH_2), 33.9 (CH_2), 37.9 (CH), 43.6 (CH), 48.3 (CH), 115.6 (CF_3) (q, $J_{C-F} = 287.3$ Hz), 156.8 (C) (q, $J_{C-F} = 37.5$ Hz) 215.2 (C). FTIR ($CHCl_3$): γ (cm^{-1}) 3312 (NH), 1770 (C=O), 1706 (C=O). HRMS found: *m*/*z* 221.0653; calcd for $C_9H_{10}NO_2F_3$ [M^+]: 221.0664.

4.6. (−)-2-*exo*-Trifluoroacetamide-7-*syn*-hydroxy-norbornane (−)-11

In a 100 mL three-necked round-bottomed flask under argon, a solution of compound (+)-**10** (1 g, 4.5 mmol) in dry THF (25 mL) was cooled to −78 °C and then 9 mL of a 1 M solution of L-Selectride slowly added. The mixture was stirred for 4 h at this temperature and then quenched with 1 mL of a 10% HCl solution. The mixture is extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and evaporated providing 1.3 g of an orange oil. The crude product was purified by flash chromatography (silica, cyclohexane/AcOEt 3:1) yielding 0.85 g (85%) of a light yellow oil. $[\alpha]_D^{20} = -3.6$ (*c* 1.1, AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.17 (s, 1H), 4.12 (s, 1H), 2.19 (s, 1H), 2.08 (s, 1H), 1.95 (m, 2H), 1.65 (m, 2H),

1.25 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 23.3 (CH_2), 25.1 (CH_2), 36.9 (CH_2), 40.8 (CH), 45.3 (CH), 52.3 (CH), 80.1 (CH), 116.0 (CF_3) (q, $J_{C-F} = 287.5$ Hz), 155.6 (C) (q, $J_{C-F} = 36.6$ Hz). FTIR ($CHCl_3$): γ (cm^{-1}) 3308 (OH), 1641 (C=O). HRMS found: *m/z* 223.0910; calcd for $C_9H_{13}NO_2F_3$ [M^+]: 223.1957.

4.7. (−)-2-*exo*-Amino-7-*syn*-hydroxy-norbornane (−)-12

To a stirred solution of (−)-**11** (0.7 g, 3.1 mmol) in methanol (20 mL) were added 2.1 g of K_2CO_3 (15.5 mmol) dissolved in 5 mL of H_2O. The solution was refluxed for 2 h and then evaporated. The crude mixture was treated with 2 mL of H_2O and extracted with chloroform, dried over anhydrous $MgSO_4$, filtered, and evaporated to provide 338 g (85%) of a light yellow oil. $[\alpha]_D^{20} = -5.0$ (*c* 1.2, AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 3.97 (s, 1H), 3.25 (d, 1H, $J = 6.8$ Hz), 2.20 (s, 1H), 1.91 (s, 1H), 1.78 (m, 2H), 1.58 (m, 2H), 1.08 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 22.9 (CH_2), 25.5 (CH_2), 37.5 (CH_2), 41.4 (CH), 44.8 (CH), 55.1 (CH), 81.1 (CH). FTIR ($CHCl_3$): γ (cm^{-1}) 3327 (OH/NH). HRMS found: *m/z* 127.0996; calcd for $C_7H_{13}NO$ [M^+]: 127.0997.

4.8. (+)-2-*exo*-Acetamide-7-*syn*-acetate-norbornane (+)-13

Compound (−)-**12** (0.37 g, 3 mmol) was dissolved in acetic anhydride (16 mL) and refluxed for 4 h. The mixture was neutralized with a 10% $NaHCO_3$ solution and extracted with chloroform, dried over anhydrous $MgSO_4$, filtered, and evaporated to provide 0.54 g (87%) of a yellow solid. Mp: 98–99 °C. $[\alpha]_D^{20} = +22.0$ (*c* 1.2, AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.82 (s, 1H), 4.08 (m, 1H), 2.33 (s, 1H), 2.25 (s, 1H), 2.14 (s, 3H), 2.10 (m, 2H), 2.04 (s, 3H), 1.64 (m, 2H), 1.25 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 21.1 ($2CH_3$), 23.3 (CH_2), 24.6 (CH_2), 37.4 (CH_2), 38.3 (CH), 43.8 (CH), 51.7 (CH), 81.5 (CH), 168.5 (C), 169.8 (C). FTIR ($CHCl_3$): γ (cm^{-1}) 3313 (NH), 1738 (C=O), 1645 (C=O). HRMS found: *m/z* 211.1213; calcd for $C_{11}H_{17}NO_3$ [M^+]: 211.1208.

4.9. (−)-2-*exo*-Ethylamino-7-*syn*-hydroxy-norbornane (−)-14

In a 100 mL three-necked round-bottomed flask under argon, $LiAlH_4$ (0.36 g, 9.6 mmol) was suspended in dry THF (20 mL). Compound (+)-**13** (0.52 g, 2.4 mmol) was dissolved in dry THF, added dropwise and the resulting mixture refluxed for 4 h. The solution was cooled to 0 °C, quenched slowly with a 10% NaOH solution (1 mL) and diluted with chloroform (30 mL). The solution was stirred over night at room temperature, filtered, dried over anhydrous $MgSO_4$, filtered, and evaporated to provide 0.35 g (93%) of a yellow oil. $[\alpha]_D^{20} = -20.0$ (*c* 1.0, AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 3.86 (s, 1H), 2.84 (m, 1H), 2.60 (q, 2H, $J = 7.3$ Hz), 2.09 (s, 1H), 1.92 (s, 1H), 1.60 (m, 2H), 1.54 (m, 2H), 1.19 (s, 2H), 1.1.03 (t, 3H, $J = 7.1$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 15.0 (CH_3), 22.9 (CH_2), 25.8 (CH_2), 35.8 (CH_2), 40.8 (CH), 41.3 (CH_2), 42.4 (CH), 61.9 (CH), 80.7 (CH). FTIR ($CHCl_3$): γ (cm^{-1}) 3293 (OH). HRMS found: *m/z* 155.1292; calcd for $C_9H_{17}NO$ [M^+]: 155.1310.

4.10. (+)-2-*exo*-Acetylethylamino-7-*syn*-acetate-norbornane (+)-15

Compound (−)-**14** (0.35 g, 2.2 mmol) was dissolved in acetic anhydride (15 mL) and refluxed for 4 h. The mixture was neutralized with a 10% $NaHCO_3$ solution and extracted with chloroform, dried over anhydrous $MgSO_4$, filtered, and evaporated to provide 0.51 g (96%) of a yellow oil. $[\alpha]_D^{20} = +2.0$ (*c* 1.1, AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.67 (s, 1H), 4.09 (m, 1H), 3.42 (q, 2H, $J = 7.0$ Hz), 2.22 (s, 1H), 2.15 (s, 3H), 2.14 (s, 1H), 2.03 (s, 3H), 1.98 (s, 2H), 1.21 (m, 2H), 1.07 (m, 2H). (The CH_3 from *N*-ethyl group appears only in ^{13}C.) ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 15.7 (CH_3), 21.1 (CH_3), 22.3 (CH_3), 24.2 (CH_2), 25.3 (CH_2), 35.1 (CH_2), 38.3 (CH), 38.9 (CH_2), 43.0 (CH), 57.5 (CH), 80.4 (CH), 170.1 (C), 170.7 (C). FTIR ($CHCl_3$): γ (cm^{-1}) 1733 (C=O), 1625 (C=O). HRMS found: *m/z* 239.1537; calcd for $C_{13}H_{21}NO_3$ [M^+]: 239.1521.

4.11. (−)-2-*exo*-*N*,*N*-Diethylamino-7-*syn*-hydroxy-norbornane (−)-16

In a 100 mL three-necked round-bottomed flask under argon, $LiAlH_4$ (0.39 g, 10.4 mmol) was suspended in dry THF (25 mL). Compound (+)-**15** (0.54 g, 2.6 mmol) was dissolved in dry THF and added dropwise. The resulting mixture was refluxed for 4 h. The solution was cooled to 0 °C, quenched slowly with a 10% NaOH solution (1 mL) and diluted with chloroform (30 mL). The solution was stirred over night at room temperature, filtered, dried over anhydrous $MgSO_4$, filtered, and evaporated to provide 0.36 g (92%) of a yellow oil. $[\alpha]_D^{20} = -41.0$ (*c* 1.1, AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 3.92 (s, 1H), 2.71. (q, 4H, $J = 7.1$ Hz), 2.34 (s, 1H), 2.16 (s, 1H), 1.93 (m, 2H), 1.63 (m, 2H), 1.16 (m, 2H), 1.04 (t, 6H, $J = 7.1$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 10.9 ($2CH_3$), 23.7 (CH_2), 25.7 (CH_2), 34.3 (2 CH_2), 40.0 (CH), 41.2 (CH), 43.2 (CH_2), 65.5 (CH), 80.8 (CH). FTIR ($CHCl_3$): γ (cm^{-1}) 3323 (OH). HRMS found: *m/z* 183.1627; calcd for $C_{11}H_{21}NO$ [M^+]: 183.1623.

4.12. (−)-2-*exo*-*N*,*N*-Dimethylamino-7-*syn*-hydroxy-norbornane (−)-17

To 140 mg (1.1 mmol) of (−)-**12**, 2 mL of formaldehyde (36% H_2O solution) and 8 mL of 85% formic acid were added. The solution was refluxed for 7 days. The resulting mixture was cooled to 0 °C, made alkaline by the addition of 20% NaOH (pH = 10) and extracted with Et_2O. The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated. The crude product was purified by silica gel chromatographic column ($CHCl_3$/MeOH 9:1) giving 102 mg (60%) of yellow oil. $[\alpha]_D^{20} = -25.0$ (*c* 1.2, AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 3.80 (1H), 2.21 (d, 1H, $J = 6.0$ Hz), 2.14 (s, 6H), 2.05 (m, 2H), 1.80 (m, 2H), 1.45 (m, 2H), 1.00 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 23.3 (CH_2), 25.4 (CH_2), 34.0 (CH_2), 40.1 (CH), 41.0 (CH), 43.4 (CH), 71.0 ($2CH_3$), 80.5 (CH). IV ($CHCl_3$): (cm^{-1}) 3403 (OH). HRMS found: *m/z* 155.1324; calcd for $C_9H_{17}NO$ [M^+]: 155.1310.

4.13. (−)-2-*exo*-Piperidine-7-*syn*-hydroxy-norbornane (−)-18

To a solution of 107 mg (0.8 mmol) of (−)-**12** in acetonitrile, 0.14 mL (0.92 mmol) of 1,5-diiodopentane and 290 mg (2.1 mmol) of K_2CO_3 were added and the solution refluxed for 1 h. The mixture was filtered and the excess of acetonitrile was evaporated. The residue was washed with 5 mL of H_2O and extracted with chloroform. The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent evaporated to give 100 mg of a yellow oil (65%). $[\alpha]_D^{20} = -30.0$ (*c* 1.0, AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.00 (s, 1H), 2.57 (s, 1H), 2.18 (m, 2H), 1.62 (m, 10H), 1.22 (m, 2H), 1.1 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 23.5 (CH_2), 23.7 ($2CH_2$), 24.7 (CH_2), 25.3 (CH_2), 29.6 (CH_2), 33.5 ($2CH_2$), 39.8 (CH), 40.8 (CH), 70.1 (CH), 79.8 (CH). IV ($CHCl_3$): (cm^{-1}) 3395 (OH). HRMS found: *m*/*z* 195.1614; calcd for $C_{12}H_{21}NO$ [M^+]: 195.1623.

4.14. (−)-2-*exo*-Acetamide-7-*syn*-hydroxy-norbornane (−)-19

To a solution of 180 mg (0.84 mmol) of (+)-**13** in 5 mL of THF, 6 mL of 20% HCl solution is added and the solution is stirred for 15 h. The mixture is neutralized with a 10% $NaHCO_3$ solution and extracted with Et_2O. The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated to give 135 mg of a yellow solid (95%). Mp: 101–102 °C. $[\alpha]_D^{20} = +5.4$ (*c* 1.1, AcOEt). ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 4.15 (s, 1H), 3.48 (s, 1H), 2.20 (s, 2H), 2.00 (s, 3H), 2.75 (m, 2H), 2.60 (m, 2H), 2.45 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 23.5 (CH), 23.8 (CH_2), 25.2 (CH_2), 37.5 (CH_2), 40.9 (CH), 45.5 (CH), 51.8 (CH), 79.9 (CH), 168.8 (C). IV ($CHCl_3$): (cm^{-1}) 3308 (OH), 1641, (C=O). HRMS found: *m*/*z* 169.1109; calcd for $C_9H_{15}NO_2$ [M^+]: 169.1103.

4.15. General procedure for the enantioselective addition of diethylzinc to benzaldehyde

To the catalyst (19 mg, 0.1 mmol) dissolved in toluene (4 mL), diethylzinc (1.2 mL, 1 M in hexane) was slowly added. The resulting solution was stirred for 2 h at room temperature and then benzaldehyde (0.052 mL, 0.5 mmol) was added dropwise. The reaction mixture was stirred at room temperature and monitored by GC. The reaction was quenched with aqueous HCl (10%, 5 mL) and extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated in vacuum to give the crude reaction mixture which was analyzed by GC.

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