Tetrahedron: *Asymmetry* 19 (2008) 1484–1493

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

New bicyclic γ- and δ-aminoalcohols as catalysts for the asymmetric diethylzinc addition to benzaldehyde

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ARTICLE INFO

Article history:
Received 5 May 2008
Accepted 2 June 2008

ABSTRACT

A new class of chiral non-racemic γ- and δ-amino alcohols based on bicyclo[2.2.1]heptane and bicyclo[2.2.2]octane have been synthesized and used as catalysts in the asymmetric diethylzinc addition to benzaldehyde.

1. Introduction

Since 1984, when Oguni et al. used (*S*)-leucinol in a catalytic amount to obtain moderate enantiomeric excess in the addition of diethyl zinc to benzaldehyde,[1] there has been a remarkable number of chiral ligands developed for this reaction.[2–4] The diethylzinc addition has become one of the most used 'test reactions' for the asymmetric induction of new metal coordinated ligands and catalysts. To reduce the number of possible close energy diastereomeric transition states many of the ligands make use of a rigid backbone. Bicyclic frameworks could be very useful for this purpose and many ligands of this type have been tested. The most well-known is DAIB [(−)-3-*exo*-(dimethylamino)isoborneol], which was the first ligand to give high enantioselectivity in the diethylzinc addition to benzaldehydes.[5] Many of the bicyclic ligands are developed from the chiral pool[6–9] (i.e., camphor or fenchone) but there are also examples of de novo synthetic ligands.[10–12] The advantage of the non-natural ligands is that both enantiomers are often available. A variety of chiral diols, amino alcohols, diamines, and amino thiols have been tested as catalysts in the reaction, but the majority are β-amino alcohols. The γ- and δ-aminoalcohols are less frequent but there has been increased interest in them recently.[9]

We recently reported the influence of various bicyclic diols on the enantioselectivity in the diethylzinc addition to benzaldehyde.[13,14] We found that the key features of an efficient catalyst were the presence of a third coordinating group and the distance between the coordinating groups. Starting from the same optically active material as used for the diol-synthesis, a new series of bicyclic aminoalcohols were synthesized. Herein, we present the synthesis of bicyclo[2.2.1]heptane-2,5-aminoalcohols (BHEPTAMOLs)[†] and bicyclo[2.2.2]octane-2,6-aminoalcohols (BOCTAMOLs).[‡] The catalytic ability of these amino alcohols toward the enantioselective addition of diethylzinc to benzaldehyde was evaluated. Due to a less than convenient synthesis, the bicyclo[2.2.2]octane-2,5-aminoalcohols and bicyclo[2.2.1]heptane-2,6-aminoalcohols have not been included in this study.

2. Results and discussion

2.1. Synthesis of 2,5-BHEPTAMOLs

A four-step synthesis to the BHEPTAMOLs was used, as is described below. Aryl-substituted hydroxy ketones (−)-**6**–(−)-**9** were synthesized by the addition of organolithium or Grignard reagents to optically active hydroxy ketone (−)-**1**, followed by TPAP/NMO oxidation as previously described by our group.[13] Reaction of the ketones with benzylamine, followed by azeotropic removal of water, gave the corresponding benzylimines, which were reduced with $NaBH_4$ to give *endo*-amines (−)-**10**–(−)-**13**, selectively, while one-pot reductive amination of (−)-**6** in the presence of $NaBH_3CN$ or $NaBH(OAc)_3$ gave the *endo*- and *exo*-aminoalcohol isomers in 90:10 and 70:30 ratios, respectively. The lower selectivities in these cases were probably caused by the anchoring effect of the hydride reagent to the alcohol, since $NaBH_4$ only gave reduction from the less sterically hindered *exo*-face.[15,16] We also wanted to test some tertiary amines corresponding to secondary amines (−)-**10**–(−)-**13**. A method for the alkylation of secondary amines without the formation of quaternary ammonium salts, using 1.1 equiv of an alkylbromide and 1.5 equiv of Hünig's base in CH_3CN, was found in the literature.[17] In our cases, however, for

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[†] We suggest that the aminoalcohols based upon the bicyclo[2.2.1]heptane framework should be named BHEPTAMOLs (*bi*cyclo[2.2.1]*hept*ane*am*inoalcoh*ols*).

[‡] We suggest that the aminoalcohols based upon the bicyclo[2.2.2]octane framework should be named BOCTAMOLs (*bi*cyclo[2.2.2]*oct*ane*am*inoalcoh*ols*).

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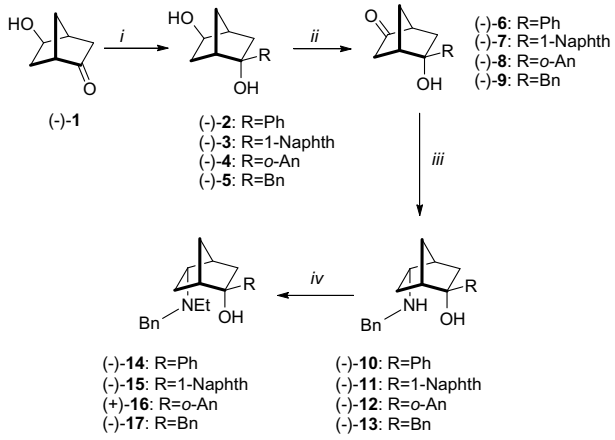
doi:10.1016/j.tetasy.2008.06.002

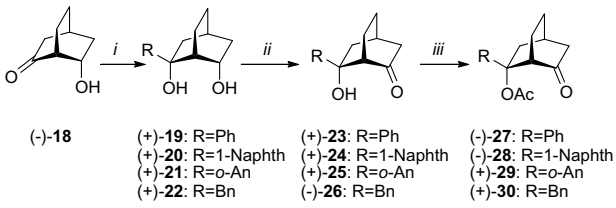
the ethylation of aminoalcohols (−)-**10**–(−)-**13**, the amount of EtBr was increased to 10 equiv to obtain complete conversion without significant amounts of quarternization. Thus, tertiary aminoalcohols (−)-**14**–(−)-**17** were isolated in 70–93% yield (Scheme 1).



Scheme 1. Reagents and conditions: (i) RMgX/RLi, THF, 0 °C (63–82%); (ii) TPAP, NMO, CH_2Cl_2, MS 4 Å, rt (85–95%); (iii) (a) $BnNH_2$, toluene, reflux, 5 h; (b) $NaBH_4$, MeOH, 0 °C, then rt, 15 min (64–97%); (iv) EtBr, Hünig's base, CH_3CN, overnight, 80 °C (70–93%).

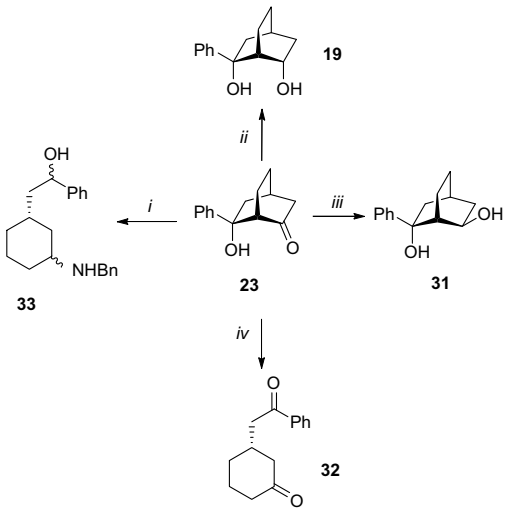
2.2. Synthesis of 2,6-BOCTAMOLs

We attempted to synthesize 2,6-BOCTAMOLs by the same procedure that was used for the synthesis of 2,5-BHEPTAMOLs. Aryl-substituted diols (+)-**19**–(+)-**22** were synthesized by the addition of organolithium or Grignard reagents to optically active hydroxy ketone (−)-**18**, as previously described.[18] The diols were oxidized with TPAP/NMO to give hydroxy ketones (+)-**23**–(+)-**26** (Scheme 2).



Scheme 2. Reagents and conditions: (i) RMgX or RLi, Et_2O/THF (65–94%); (ii) TPAP, NMO, MS 4 Å, CH_2Cl_2, rt, 1 h (87–90%); (iii) Ac_2O, DMAP, pyridine, 60 °C, 1.5–7 days (47–72%).

We attempted to synthesize **36** (Scheme 4) from **23** by using the same two-step procedure as we had used for the [2.2.1]-system described above. Disappointingly, this resulted in an isomeric mixture of **33**, caused by a retro-aldol reaction, which opened the bicyclic ring (Scheme 3). Reaction of hydroxy ketone **23** with $NaBH_4$ resulted only in diol **19**, but no ring-opening products were observed. Thus, we suspected that the imine, and not the reducing agent, caused the ring-opening. Indeed, the formation of the imine followed by hydrolysis resulted in ring-opened diketone **32**. Lower reaction temperature (using MS 4 Å, Na_2SO_4 or KOH as drying agents) did not prevent ring-opening. It only led to incomplete consumption of the reagent or formation of several by-products. Even if reductive amination with $NaBH_3CN$ or $NaBH(OAc)_3$ were expected to give less selective reduction, we hoped that these reagents would prevent ring-opening. However, the reaction of hydroxy ketone **23** with benzylamine and $NaBH(OAc)_3$ in THF at rt gave diol **31**, formed by *endo*-face reduction of the hydroxy ketone. This clearly shows the anchoring effect of $NaBH(OAc)_3$ to



Scheme 3. Reagents and conditions: (i) (a) $BnNH_2$, toluene, reflux; (b) $NaBH_4$, MeOH, 0 °C; (ii) $NaBH_4$, MeOH, 0 °C; (iii) $BnNH_2$, $NaBH(OAc)_3$, THF, rt; (iv) (a) $BnNH_2$, toluene, reflux; (b) H_2O.

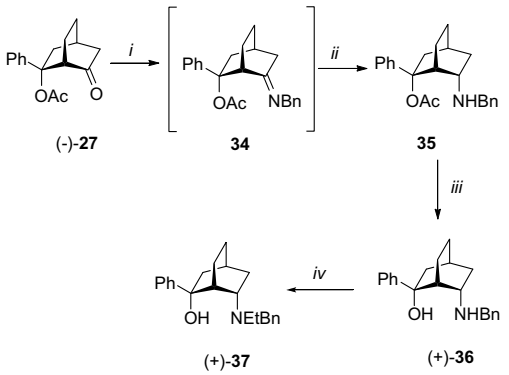
the hydroxyl group.[16,15] TLC analysis of the reaction mixture from reductive amination using $NaBH_3CN$ in THF showed a very unselective reaction.

We concluded that the only way to prevent the retro-aldol reaction was to protect the alcohol before the imine synthesis. Standard methods for MEM- and TBDMS-protection failed.[19,20] We then turned to protection by acylation. Reaction of hydroxy ketones (+)-**23**–(+)-**26** with acetic anhydride in pyridine with catalytic amounts of DMAP, according to a literature procedure,[21] gave the keto esters (−)-**27**–(+)-**30** in 47–72% yield (Scheme 2). We were puzzled by the relatively low yields, since TLC-analysis of the reaction mixture showed rather clean reactions. We speculated that the low yields were mainly caused by polymerization of the reactant and/or the product.

In the reaction of phenyl-, 1-naphthyl-, and benzyl-substituted hydroxy ketones (+)-**23**, (+)-**24**, and (+)-**26**, small amounts (>10%) of the corresponding unsaturated ketones from elimination of the alcohol or ester were observed by NMR-analysis of the crude products. However, for the *o*-anisyl-substituted hydroxy ketone (−)-**25**, the corresponding unsaturated ketone was isolated in 30% yield. Acylation involving either $Sc(OTf)_3$[22] or TMSOTf[23] gave the unsaturated ketone as the main product.

Naphthyl-substituted acetate (−)-**28** appeared as rotamers in solution (in benzene and in $CHCl_3$) and therefore gave considerably broadened NMR-signals. The chemical shifts of some protons and the coupling pattern changed when the NMR-sample was heated to 343 K, but the signals remained broad. Additional structural evidence of this compound was established from the mass-spectral fragmentation pattern (EI).

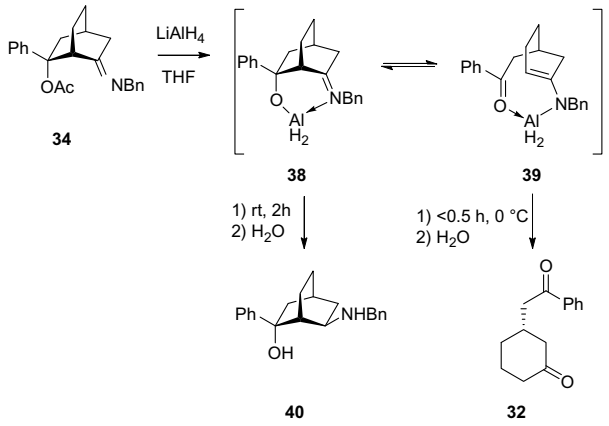
Imine formation was now successful; reaction of ketoacetate (−)-**27** with 5 equiv of benzylamine, 2 equiv of acetic acid, and MS 4 Å in toluene at 80 °C gave high conversion to imine **34** (Scheme 4). The addition of acetic acid was crucial for the reaction to proceed and it was important to have an excess of benzylamine in relation to acetic acid to avoid side reactions caused by elimination. Reduction of the imine with $NaBH_4$ in methanol gave compound **35**. Despite repeated column chromatography, compound **35** could not be separated from *N*-benzyl-acetamide formed in the reaction. Therefore, the crude product of **35** was reacted directly with $LiAlH_4$ to cleave off the acetate, which gave aminoalcohol (+)-**36** in 91% yield. Finally, compound (+)-**37** was obtained by reaction of (+)-**36** with ethylbromide and Hünig's base, as



Scheme 4. Reagents and conditions: (i) $BnNH_2$, AcOH, toluene, 4 Å MS, 80 °C, 1–2 days; (ii) $NaBH_4$, MeOH, 0 °C; (iii) $LiAlH_4$, THF, 0 °C (91% over three steps); (iv) EtBr, Hünig's base, CH_3CN, 3 days (70%).

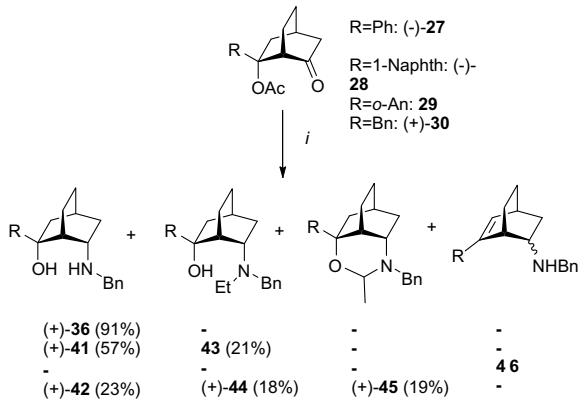
described above. Other methods to remove the ester function in **35** (NaOH in aq ethanol, $MeNH_2$ in ethanol, KCN in ethanol) resulted in the formation of one unknown compound; possibly the amide, formed by migration of the acyl group from the oxygen to the nitrogen. However, due to considerable broadening of the NMR-signals the compound was not identified.

Direct reduction of the imine and ester functions of **34** with $LiAlH_4$ resulted in *exo*-amine **40** (Scheme 5) instead of the desired aminoalcohol **36**. TLC analysis of the reaction over time showed initially that another product was formed, which was identified as diketone **32** upon hydrolysis. When the reaction was allowed to run for 2 h at rt, the only isolated product was **40**. This shed some light on the reaction mechanism. Apparently, the ester was cleaved off before the reduction of the imine. The initially formed aluminumhydride-alkoxide **38** may undergo ring-opening analogous to the retro-aldol reaction. This would generate Al-coordinated enaminoketone **39**. However, due to coordination by aluminum to nitrogen and the carbonyl, reduction of the carbonyl was slow and **39** could equilibrate back to bicyclic structure **38**. This coordination also explains why no inversion at C2 was observed, which would be expected if there had been a free rotation of the carbonyl unit. Ring-opened structure **39** was the kinetic product and hydrolysis at an early stage resulted in compound **32**. When the reaction was allowed to run for a longer time, the imine was eventually reduced from the *endo*-face by the coordinated hydridoaluminate, giving the aminoalcohol **40**.



Scheme 5. Reduction of **34** with $LiAlH_4$.

The route developed for the synthesis of aminoalcohol (+)-**36**, starting from ketoacetate (−)-**27**, was applied to 1-naphthyl-, benzyl-, and *o*-anisyl-substituted ketoacetates (−)-**28**–(+)-**30** (Scheme 6). Unfortunately, the *o*-anisyl-substituted aminoalcohol could not be obtained due to the complete elimination of acetic acid during the imine synthesis. The only isolated product was **46**. For the reaction of 1-naphthyl-substituted ketoacetate (−)-**28**, tertiary aminoalcohol **43** was isolated in 21% yield, along with the expected product (+)-**41** in 57% yield. Evidently, the acyl group had migrated from the hydroxyl group to the aminogroup, giving the corresponding acetamide derivative, which was reduced with $LiAlH_4$ to the *N*-ethyl amine. The same reactions occurred during the synthesis of benzyl-substituted aminoalcohol (+)-**42**. Compound (+)-**42** was isolated in 23% yield, along with tertiary aminoalcohol (+)-**44** in 18% yield and tricyclic structure (+)-**45** in 19% yield. According to TLC-analysis, compound (+)-**45** was formed during the $NaBH_4$ reduction. The migration of the acyl group occurred via a six-membered transition state and clearly depended on the size of the side group, since no migration was observed with the phenyl substituent. Large substituents should decrease the distance between the nitrogen and oxygen and thus promote the migration. If the migration occurred after the reduction by $NaBH_4$ an increased reaction time would promote the formation of the amide and hence the reaction could be controlled to give the tertiary aminoalcohol after reduction by $LiAlH_4$. However, these aspects have not been investigated.



Scheme 6. Reagents and conditions: (i) (1) $BnNH_2$, AcOH, toluene, MS 4 Å, 80 °C, 2 days; (2) $NaBH_4$, MeOH, 0 °C, then rt, 15 min; (3) $LiAlH_4$, THF, 0 °C, 40 min.

2.3. Catalysis

The diethylzinc additions to benzaldehyde were performed at rt in THF for 48 h in the presence of 10 mol % of the aminoalcohols. The results from the reactions are summarized in Table 1. When the reaction temperature was decreased to 0 °C, it resulted in only a slight increase in ee [from 64% to 67% for catalyst (+)-**10**] but gave a slower conversion. Numerous reports in the literature show that the best results for the reactions catalyzed with amino alcohols are achieved in diethyl ether or hydrocarbon solvents, because of the high background reaction in coordinating solvents such as THF.[5] However, with catalyst (+)-**10**, the reactions performed in hexane, diethyl ether/hexane, and toluene/hexane at 0 °C gave inferior results (40–44% ee) compared to the reaction in THF (entry 1, 64%). The results were surprising, since the background reaction in THF, without the addition of a catalyst, gave 34% yield, which showed a considerable competing reaction catalyzed by THF. With aminoalcohol (+)-**37**, however, the choice of solvents did not affect either the yield or the enantioselectivity (entry 12). The amount of catalyst (+)-**37** was reduced to 5 mol % without any influence on either the conversion or the enantioselectivity, whereas 2 mol % of the catalyst gave 74% ee and 42% yield, and 0.5 mol % of the catalyst gave only 29% yield and 10% ee.

Table 1
Application of bicyclic amino alcohols as catalysts in the addition of diethylzinc to benzaldehyde

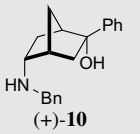
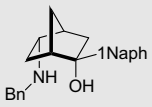
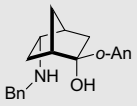
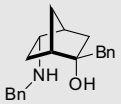
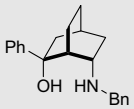
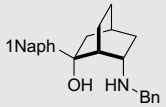
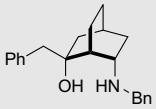
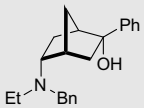
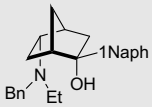
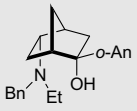
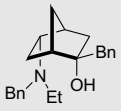
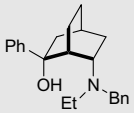
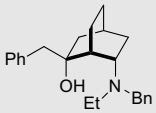
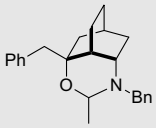
Entry	Catalyst	ee[a] of 1-phenylpropanol (%)	Yield[a] of 1-phenylpropanol (%)	Config.[b] of 1-phenylpropanol
1	 (+)-**10**	64	82	(*R*)
2	 (−)-**11**	42	88	(*S*)
3	 (−)-**12**	66	65	(*S*)
4	 (−)-**13**	82	87	(*S*)
5	 (+)-**36**	58	62	(*R*)
6	 (+)-**41**	56	42	(*R*)
7	 (+)-**42**	48	76	(*R*)
8	 (+)-**14**	74	84	(*R*)
9	 (−)-**15**	56	92	(*S*)
10	 (+)-**16**	40	50	(*S*)
11	 (−)-**17**	86	92	(*S*)
12	 (+)-**37**	89	90	(*R*)

Table 1 (*continued*)

Entry	Catalyst	ee[a] of 1-phenylpropanol (%)	Yield[a] of 1-phenylpropanol (%)	Config.[b] of 1-phenylpropanol
13	 (+)-**44**	74	89	(*R*)
14	 (+)-**45**	*rac*	44	—

[a] Determined by GC analysis using a chiral Supelco betaDEX column. The yields were calculated from the peak area given by simple integration using 1-decanol as the internal standard.
[b] Determined by the order of elution on the Supelco betaDEX column.

Generally, as expected from reports in the literature,[2] the enantioselectivity increased when the degree of *N*-alkyl substitution increased. This was especially noticeable for the phenyl-substituted BOCTAMOLs (+)-**36** and (+)-**37** when the ee was improved from 58% with the secondary aminoalcohol (+)-**36** (entry 5) to 89% with the tertiary aminoalcohol (+)-**37** (entry 12), which also represents the highest selectivity in this study. The only exception to this observation was the *o*-anisyl-substituted BHEPTAMOLs. The secondary amino alcohol (−)-**12** gave 66% ee while the tertiary amino alcohol (+)-**16** gave only 40% ee (entries 3 and 10). In the series of BHEPTAMOLs the highest ee (86%) was obtained with the benzyl-substituted derivative (−)-**17** (entry 11). The comparable selectivities for the phenyl- and the *o*-anisyl-substituted catalysts (+)-**10** and (−)-**12** (entries 1 and 3) were in contrast to the results obtained with the bicyclic diols (BODOLs) previously reported by our group.[14,13] The presence of the methoxy group of the *o*-anisyl substituent had a considerable positive impact on the selectivity. As expected, the tricyclic structure (+)-**45** was inefficient as a catalyst since it lacked the hydroxyl group, which is supposed to react with diethylzinc providing the ethylzinc alkoxide, generally being considered the active catalyst.[2,24]

For the two series, different side groups gave the best results. In the [2.2.1]-series (−)-**17** (entry 11), carrying the benzyl side group, was the best catalyst, while in the [2.2.2]-series (+)-**37** (entry 12), carrying the phenyl side group, was the best catalyst. There was otherwise no general trend that one of the backbones was better than the other for achieving efficient catalysis, despite different distances between the coordinating groups.

Martinez et al. presented a qualitative empirical explanation to the observed enantioselectivity imposed by norbornane-derived β-, γ-, and δ-aminoalcohols (Fig. 1).[9] The study was based on the Noyori model suggesting that the β-aminoalcohol **47** gave a 5/4/4 transition state, the γ-amino alcohol **48** a tricyclic 6/4/4 transition state, and the δ-amino alcohol **49** a 7/4/4 transition state. Thus, the BOCTAMOLs were expected to form a six-membered zinc-chelate and the BHEPTAMOLs a seven-membered ring zinc-chelate (Fig. 2).

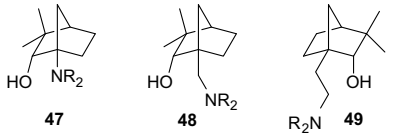


Figure 1. β-, γ-, and δ-aminoalcohols developed by Martinez et al.[9]

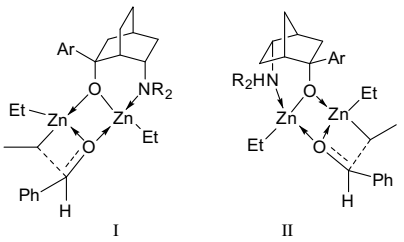


Figure 2. The suggested 6/4/4 TS of BOCTAMOLs (I) and 7/4/4 TS of BHEPTAMOLs (II).

The positioning of the amine and the hydroxyl groups directly at the bicyclic backbone in our catalysts would decrease the conformational flexibility of the six- and seven-membered rings, plausibly giving rise to fewer possible diastereomeric transition states. We made simple models of the suggested 6/4/4 and 7/4/4 arrangements to try to gain some insight in the enantioselection given by our systems. We set the O–Zn bond to be 2 Å and took into consideration the sterical interactions and the orientation of the electron-pairs involved in the bond-formation to identify the most energetically favored transition structures. However, we found several possible structures resulting in the opposing configuration of the 1-phenylpropanol. Since this was contradicted by the experimental results, which clearly show moderate to high enantioselectivity for all catalysts, this simple study was not enough to explain the experimental results. Thorough computational calculations on the proposed transition states and other possible structures, such as the 6/6 and 7/6 bicyclic transition states as suggested by Norrby et al.,[25] would hopefully give results consistent with the experimental results.

3. Conclusion

In conclusion, the presented results demonstrate that 2,5-BHEPTAMOLs and 2,6-BOCTAMOLs are efficient catalysts in the diethylzinc addition to benzaldehyde, which indicates that the formation of aminoalcohol–zinc chelates was not particularly sensitive to the distance between the coordinating groups. These results stand in contrast to results given by similar bicyclic diols, previously studied by our group, where a longer distance between the coordinating groups was detrimental for the catalytic efficiency.[13] Generally the tertiary aminoalcohols gave higher ee than the corresponding secondary aminoalcohols. Otherwise, no clear structural features could be discerned. In the series of BHEPTAMOLs the benzyl-substituted catalyst (−)-**17** gave the highest ee and in the series of BOCTAMOLs the phenyl-substituted catalyst (+)-**37** gave the highest ee. The synthesis of the 2,5-BHEPTAMOLs was rather straightforward, while the synthesis of the 2,5-BOCTAMOLs was complicated by competing retro-aldol reaction, elimination reactions, and migration of functional groups.

4. Experimental

4.1. General

All reactions were carried out in oven-dried glassware under a nitrogen atmosphere. THF and diethyl ether was distilled from sodium and benzophenone and benzaldehyde and benzylamine were distilled prior to use. Bicyclic compounds **1**, **2**, **3**, **4**, **6**, **7**, **8**[13] and **19**, **20**, and **21**[18] were synthesized according to previous procedures. All reagents were purchased from Aldrich and used as received. TLC was carried out on Silica Gel (60 F_{254}, Merck) and spots were visualized with UV light or by staining with a solution of $H_3[P(Mo_3O_{10})_4]$ (25 g), $Ce(SO_4)_2$ (10 g), and concd H_2SO_4 (60 mL) in H_2O (940 mL) or with a solution of *p*-methoxybenzaldehyde (10 mL), concd H_2SO_4 (50 mL), and ethanol (95%, 940 mL). Flash chromatography was performed on Matrex (25–70 μm) silica gel. GC analyses were performed on a betaDEX column (Supelco, 30 m × 0.25 mm id, 25 μm film thickness). NMR spectra were recorded on a Bruker DRX 400 MHz spectrometer, using the residual solvent as internal standard. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter at 20 °C and are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a Shimadzu 8300 FTIR spectrometer. Melting points were taken on a Sanyo Gallenkamp melting point apparatus (MPD.350.BM3.5) and are uncorrected. Elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Höhenweg 17, D-45470 Mülheim an der Ruhr.

4.2. General procedure: addition of Et_2Zn to benzaldehyde

The catalyst (10 mol %) was dissolved in dry THF (0.7 mL), and diethylzinc (1.0 M in hexane, 1 mL, 1.0 mmol) was added at rt. The mixture was stirred for 30 min, and then freshly distilled benzaldehyde (51 μL, 0.5 mmol) was added. The reaction was stirred under a flow of N_2 at rt for 48 h then satd aqueous NH_4Cl was added. Dichloromethane (10 mL) was used to extract the aqueous phase on an Isolute® Phase Separator column. Yields and ee were analyzed by GC on a Supelco betaDEX column (isothermal at 130 °C). 1-Octanol was used as internal standard. The retention times were benzaldehyde 4.6 min, benzylalcohol 9.3 min, 1-decanol 13.7 min, (*R*)-1-phenylpropanol 14.1 min, and (*S*)-1-phenylpropanol 14.8 min.

4.3. (1*S*,2*R*,4*S*,5*R*)-2-Benzyl-bicyclo[2.2.1]heptan-2,5-diol (−)-5

A solution of (−)-**1** (0.30 g, 2.3 mmol) in dry THF (8 mL) was added to BnMgCl (1.0 M in ether, 7.3 mL, 7.3 mmol) at 0 °C under a nitrogen atmosphere. The resulting slurry was stirred at rt for 16 h then water was added. The mixture was worked up as follows: extraction with EtOAc, washing of the collected organic phases with satd aqueous $NaHCO_3$ and brine followed by drying over Na_2SO_4 and removal of the solvent under reduced pressure. The residue was recrystallized from toluene to give (−)-**5** (0.32 g, 63%, 96% ee) as white crystals; TLC R_f 0.5 (CH_2Cl_2–*i*PrOH, 90:10); mp 131–133 °C; $[\alpha]_D^{20} = -18$ (*c* 1.0, $CHCl_3$); IR (KBr) 3298 cm^{-1}; ^{1}H NMR (400 MHz, pyridine-d_5) δ 1.30 (1H, dd, *J* = 13.0, 2.8 Hz), 1.57 (1H, dt, *J* = 12.5, 3.4 Hz), 1.74 (1H, dm, *J* = 10.1 Hz), 1.86 (1H, dd, *J* = 13.0, 5.1 Hz), 2.10–2.12 (1H, dm, *J* = 10.0 Hz), 2.33 (1H, d, *J* = 3.8 Hz), 2.44 (1H, d, *J* = 4.8 Hz), 2.95–3.00 (1H, m), 3.01 (1H, d_{AB}, J_{AB} = 13.6 Hz), 3.09 (1H, d_{AB}, J_{AB} = 13.6 Hz), 4.31 (1H, d, *J* = 6.1 Hz), 5.55 (1H, br s), 6.00 (1H, br s), 7.25–7.29 (1H, m), 7.34–7.39 (2H, m), 7.54–7.59 (2H, m); ^{13}C NMR (100 MHz, pyridine-d_5) δ 35.4, 36.2, 42.4, 46.7, 46.9, 49.0, 74.2, 78.6, 126.8, 128.7, 131.9, 140.0; HRMS (FAB+) [M−OH]: calcd for $C_{14}H_{17}O$: 201.1274, found: 201.1292. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.93; H, 8.35.

4.4. (1*R*,2*S*,4*S*,6*S*)-2-Benzyl-bicyclo[2.2.2]octane-2,6-diol (+)-22

A solution of 2.0 M BnMgCl in THF (17.5 mL, 35 mmol) was added to a solution of (−)-**18** (2.0 g, 14 mmol) in diethyl ether (150 mL) at 0 °C. The mixture was stirred at rt for 45 min then satd aqueous NH_4Cl (100 mL) was added. The reaction was worked up as follows: extraction with diethyl ether, washing of the collected organic phases with brine followed by drying over Na_2SO_4, and removal of the solvent under reduced pressure. The residue was recrystallized from heptane–EtOAc, and the mother liquor was purified by column chromatography (SiO_2, heptane–EtOAc, 75:25) to give (+)-**22** (1.43 g, 89%) in 99% ee as white crystals;

TLC R_f 0.5 (heptane–EtOAc, 1:1); mp 86–87 °C; $[\alpha]_D^{20} = +61$ (*c* 1.05, $CHCl_3$); IR (KBr) 3208 (br) cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 1.00–1.07 (3H, m), 1.41–1.53 (6H, m), 1.84–1.90 (1H, m), 2.50–2.53 (2H, m), 2.74 (1H, d_{AB}, J_{AB} = 13.6 Hz), 3.18 (1H, s), 3.58–3.62 (1H, m), 7.10–7.15 (1H, m), 7.17–7.21 (2H, m), 7.26–7.28 (2H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 21.3, 23.7, 26.5, 38.0, 39.4, 45.1, 48.5, 71.3, 74.9, 126.9, 128.7, 131.4, 138.3; HRMS (FAB+) [M+Na]: calcd for $C_{15}H_{20}O_2Na$: 255.1361, found: 255.1368. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.51; H, 8.62.

4.5. (1*S*,4*S*,5*R*)-5-Benzyl-5-hydroxy-bicyclo[2.2.1]heptan-2-one (−)-9

Compound (−)-**5** (0.35 g, 1.6 mmol), NMO (0.37 g, 3.2 mmol), 4 Å MS, and TPAP (0.03 g, 0.08 mmol) were mixed in CH_2Cl_2 (20 mL). The resulting mixture was stirred at rt for 45 min, then diluted with EtOAc and filtered through Celite/silica (rinsed with EtOAc). The solvent was removed under reduced pressure and the crude product was purified by column chromatography (SiO_2, heptane–EtOAc, 7:3) to give (−)-**9** (0.33 g, 95%) in 96% ee as a white solid; TLC R_f 0.5 (heptane–EtOAc, 1:1); $[\alpha]_D^{20} = -45$ (*c* 1.1, $CHCl_3$); mp 90–93 °C; IR (KBr) 3430, 1726 cm^{-1}; ^1H NMR (400 MHz, pyridine-d_5) δ 1.69 (1H, m), 1.72 (1H, m), 1.91–2.00 (2H, m), 2.06–2.10 (1H, m), 2.57 (1H, m), 2.60 (1H, m), 2.93–2.98 (1H, dd, *J* = 17.4, 4.4 Hz), 3.06 (1H, d_{AB}, J_{AB} = 13.7 Hz), 3.14 (1H, d_{AB}, J_{AB} = 13.7 Hz), 6.26 (1H, s), 7.26–7.30 (1H, m), 7.35–7.39 (2H, m), 7.54–7.55 (2H, m); ^{13}C NMR (100 MHz, pyridine-d_5) δ 37.7, 40.3, 42.1, 46.0, 49.0, 52.2, 78.2, 127.0, 128.8, 131.8, 139.4, 217.4; HRMS (FAB+) [M+H]: calcd for $C_{14}H_{17}O_2$: 217.1229, found: 217.1230. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.86; H, 7.42.

4.6. (1*S*,4*R*,6*S*)-6-Benzyl-6-hydroxy-bicyclo[2.2.2]octane-2-one (+)-26

The title compound was synthesized following the same procedure as for (−)-**9**, from (+)-**22** (2.8 g, 12 mmol) to give (+)-**26** (2.47 g, 89%, 99% ee) as white crystals; TLC R_f 0.47 (heptane–EtOAc, 1:1); $[\alpha]_D^{20} = +46$ (*c* 0.95, $CHCl_3$); mp 115–117 °C; IR (KBr) 3428, 1717 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 1.07–1.10 (2H, m), 1.27–1.32 (1H, m), 1.36 (1H, s), 1.39–1.48 (3H, m), 1.67–1.71 (1H, m), 1.93 (1H, dt, *J* = 18.4, 2.8 Hz), 2.16 (1H, t, *J* = 2.8 Hz), 2.28 (1H, dm, *J* = 18.4 Hz), 2.46 (1H, d_{AB}, J_{AB} = 13.6 Hz), 2.53 (1H, d_{AB}, J_{AB} = 13.6 Hz), 6.95–6.98 (2H, m), 7.04–7.11 (3H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 20.0, 24.8, 28.7, 42.0, 43.6, 46.2, 53.1, 73.6, 127.4, 129.0, 131.0, 136.6, 212.0; HRMS (FAB+) [M+Na]: calcd for $C_{15}H_{18}O_2Na$: 253.1204, found: 253.1202. Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.32; H, 7.88. Found: C, 78.24; H, 7.85.

4.7. (1*S*,4*R*,6*R*)-6-Hydroxy-6-phenyl-bicyclo[2.2.2]octan-2-one (+)-23

The title compound was synthesized following the same procedure as for (−)-**9**, from (+)-**19** (1.7 g, 7.8 mmol). The crude product was purified by recrystallization from diethyl ether and column chromatography of the mother liquor (SiO_2, heptane–EtOAc, 75:25) to give (+)-**23** as white crystals (1.5 g, 90%, 99% ee); R_f 0.46 (heptane–EtOAc, 1:1); mp 102–106 °C; $[\alpha]_D^{20} = +13$ (*c* 1.0, $CHCl_3$); IR (KBr) 3337, 1713, 1697 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 1.02–1.09 (2H, m), 1.27–1.34 (2H, m), 1.64–1.71 (2H, m), 1.77–1.81 (1H, m), 1.92–1.95 (1H, m), 1.97–2.00 (1H, m), 2.41 (1H, dm, *J* = 18.4 Hz), 2.56 (1H, t, *J* = 2.8 Hz), 7.04–7.14 (3H, m), 7.18–7.22 (2H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 19.5, 24.7, 29.0, 41.6, 43.4, 55.0, 75.3, 126.4, 127.8, 128.8, 146.2, 211.4; HRMS (FAB+) [M+Na]: calcd for $C_{14}H_{16}O_2Na$: 239.1048, found: 239.1033. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.71; H, 7.44.

4.8. (1*S*,4*R*,6*R*)-6-Hydroxy-6-(1-naphthyl)-bicyclo[2.2.2]octan-2-one (+)-24

The title compound was synthesized following the same procedure as for (−)-**9**, from (+)-**20** (0.50 g, 1.9 mmol). The crude product was purified by column chromatography (SiO_2, heptane–EtOAc, 75:25) to give (+)-**24** as white crystals (0.41 g, 81%, 99% ee); TLC R_f 0.59 (heptane–EtOAc, 1:1); mp 177–180 °C; $[\alpha]_D^{20} = +14$ (*c* 0.65, $CHCl_3$); IR (KBr) 3457, 1713 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.95–1.04 (2H, m), 1.43–1.52 (1H, m), 1.56–1.64 (1H, m), 1.73–1.74 (1H, m), 1.76 (1H, s), 1.83 (1H, dm, *J* = 12.0 Hz), 1.99 (1H, dm, *J* = 18.0 Hz), 2.35 (1H, dm, *J* = 14.0 Hz), 2.52 (1H, dt, *J* = 18.4, 2.4 Hz), 3.05–3.06 (1H, m), 7.00–7.02 (1H, m), 7.09–7.13 (1H, m), 7.25–7.34 (2H, m), 7.55–7.57 (1H, m), 7.65–7.67 (1H, m), 8.82–8.84 (1H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 20.7, 25.0, 29.1, 43.5, 43.7, 54.0, 76.4, 123.4, 124.7, 126.1, 126.1, 128.7, 129.5, 129.6, 132.6, 136.2, 140.8, 211.4; HRMS (FAB+) [M+Na]: calcd for $C_{18}H_{18}O_2Na$: 289.1204, found: 289.1206. Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.11; H, 6.76.

4.9. (1*S*,4*R*,6*R*)-6-Hydroxy-6-(2-methoxy-phenyl)-bicyclo[2.2.2]octan-2-one (−)-25

The title compound was synthesized following the same procedure as for (−)-**9**, from (+)-**21** (1.0 g, 4.0 mmol). The crude product was purified by column chromatography (SiO_2, heptane–EtOAc, 1:1) to give (−)-**25** (0.86 g, 87%, 99% ee) as white crystals; TLC R_f 0.38 (heptane–EtOAc, 1:1); mp 91–94 °C; $[\alpha]_D^{20} = -33$ (*c* 1.3, $CHCl_3$); IR (KBr) 3507, 1720 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 1.08–1.28 (3H, m), 1.34–1.40 (1H, m), 1.89–1.91 (1H, m), 2.03–2.09 (2H, m), 2.24 (1H, dm, *J* = 14.8 Hz), 2.60 (1H, dt, *J* = 18.4, 2.4 Hz), 2.94 (3H, s), 3.01–3.02 (1H, m), 4.79 (1H, s), 6.38–6.41 (1H, m), 6.77–6.81 (1H, m), 6.98–7.03 (1H, m), 7.08–7.10 (1H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 19.5, 24.1, 28.3, 38.7, 43.5, 53.5, 54.4, 76.2, 111.9, 120.5, 126.8, 128.6, 131.7, 157.8, 211.4; HRMS (FAB+) [M+Na]: calcd for $C_{15}H_{18}O_3Na$: 269.1154, found: 269.1153. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.05; H, 7.27.

4.10. (1*R*,2*R*,4*R*,5*R*)-5-Benzylamino-2-phenyl-bicyclo[2.2.1]heptane-2-ol (+)-10

Benzylamine (1.0 mL, 9.1 mmol) was added to a solution of (+)-**6** (0.82 g, 4.1 mmol) in toluene (50 mL). The resulting solution was refluxed in a Dean–Stark equipment for 5 h. The mixture was cooled to rt followed by removal of the solvent under reduced pressure. The residue was dissolved in methanol (35 mL), and $NaBH_4$ (0.31 g, 8.2 mmol) was added at 0 °C. The ice-bath was removed and after 15 min, water (15 mL) was added. The methanol was removed under reduced pressure, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was column chromatographed (SiO_2, EtOAc–NH_4OH, 99:1) to give (+)-**10** (1.12 g, 96%) of >99% ee as a white solid; TLC R_f concentration dependent; mp 76–79 °C; $[\alpha]_D^{20} = +40$ (*c* 0.7, $CHCl_3$); IR (KBr) 3370, 3283 cm^{-1}; ^1H NMR (400 MHz, pyridine-d_5) δ 7.81–7.83 (2H, m), 7.53–7.54 (2H, m), 7.36–7.45 (4H, m), 7.27–7.32 (2H, m), 6.39 (1H, br s), 3.84 (1H, d_{AB}, J_{AB} = 13.2 Hz), 3.78 (1H, d_{AB}, J_{AB} = 13.2 Hz), 3.23–3.27 (1H, m), 2.57 (1H, d, *J* = 3.9 Hz), 2.40–2.44 (3H, m), 2.31 (1H, dt, *J* = 12.6 Hz, 3.4 Hz), 2.17–2.21 (1H, m), 1.85–1.89 (1H, m), 1.74–1.77 (1H, m), 1.41–1.44 (1H, m); ^{13}C NMR (100 MHz, pyridine-d_5): δ 32.3, 39.4, 40.2, 41.5, 49.2, 53.0, 58.4, 79.6, 126.9, 127.0, 127.5, 128.8, 129.1, 142.2, 151.5 (one peak

hidden by solvent); HRMS (FAB+) [M+H]: calcd for $C_{20}H_{24}NO$: 294.1858, found: 294.1852. Anal. Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90. Found: C, 81.79; H, 7.97.

4.11. (1*S*,2*S*,4*S*,5*S*)-5-Benzylamino-2-(2-methoxy-phenyl)-bicyclo[2.2.1]heptane-2-ol (−)-12

The title compound was synthesized following the same procedure as for (+)-**10**, from (−)-**8** (0.15 g, 0.6 mmol) to give (−)-**12** (0.17 g, 89%, 99% ee) as a clear oil; TLC R_f concentration dependent; $[\alpha]_D^{20} = -5$ (*c* 0.5, $CHCl_3$); IR (NaCl) 3541 cm^{-1}; ^1H NMR (400 MHz, pyridine-d_5) δ 1.41 (1H, dt_{AB}, J_{AB} = 10.1, 1.5 Hz), 1.62 (1H, dt_{AB}, J_{AB} = 10.1, 1.3 Hz), 1.87–1.94 (1H, m), 2.32 (1H, dt, *J* = 12.7, 4.7 Hz), 2.37 (1H, m), 2.53 (1H, dd_{AB}, J_{AB} = 13.9, 3.3 Hz), 2.81 (1H, d, *J* = 4.4 Hz), 3.22–3.27 (1H, m), 3.71 (3H, s), 3.80 (1H, d_{AB}, J_{AB} = 13.3 Hz), 3.87 (1H, d_{AB}, J_{AB} = 13.2 Hz), 5.12 (1H, br s), 6.98–7.05 (2H, m), 7.27–7.32 (2H, m), 7.39–7.43 (2H, m), 7.44–7.46 (1H, m), 7.53–7.58 (2H, m); ^{13}C NMR (100 MHz, pyridine-d_5) δ 31.0, 38.7, 39.2, 41.2, 46.5, 53.1, 55.7, 59.3, 79.6, 112.6, 120.9, 126.0, 127.4, 128.6, 129.0 (4C), 137.6, 142.4, 158.3; HRMS (ES+) [M−OH] calcd for $C_{21}H_{24}NO$: 306.1858, found: 306.1866. Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 78.11; H, 7.70; N, 4.26.

4.12. (1*S*,2*R*,4*S*,5*S*)-2-Benzyl-5-benzylamino-bicyclo-[2.2.1]heptan-2-ol (−)-13

The title compound was synthesized following the same procedure as for (+)-**10**, from (−)-**9** (0.22 g, 1.0 mmol) to give (−)-**13** (0.27 g, 87%, 98% ee) as a clear oil; TLC R_f was concentration dependent; $[\alpha]_D^{20} = -41$ (*c* 1.2, $CHCl_3$); IR (NaCl) 3396, 3300 cm^{-1}; ^1H NMR (400 MHz, pyridine-d_5) δ 1.41 (1H, dt, *J* = 10.2, 1.5 Hz), 1.65–1.72 (3H, m), 1.86 (1H, dd_{AB}, *J* = 13.1, 3.3 Hz), 1.99 (1H, dt, *J* = 12.5, 3.3 Hz), 2.18 (1H, d, *J* = 3.8 Hz), 2.35 (1H, m), 2.35 (1H, m), 2.94 (1H, d_{AB}, J_{AB} = 13.5 Hz), 3.06 (1H, d_{AB}, J_{AB} = 13.5 Hz), 3.14–3.19 (1H, m), 3.67 (1H, d_{AB}, J_{AB} = 13.1 Hz), 3.73 (1H, d_{AB}, J_{AB} = 13.1 Hz), 5.34 (1H, br s), 7.22–7.39 (6H, m), 7.42–7.44 (2H, m), 7.56–7.58 (2H, m); ^{13}C NMR (100 MHz, pyridine-d_5) δ 32.1, 38.5, 39.2, 41.4, 48.0, 49.0, 52.9, 58.1, 78.8, 126.7, 127.4, 128.5, 129.0, 129.0, 131.8, 139.8, 142.0; HRMS (FAB+) [M+Na]: calcd for $C_{21}H_{25}NONa$: 330.1828, found: 330.1834. Anal. Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 81.96; H, 8.24; N, 4.60.

4.13. (1*S*,2*S*,4*S*,5*S*)-5-Benzylamino-2-(1-naphthyl)-bicyclo-[2.2.1]heptan-2-ol (−)-11

The title compound was synthesized following the same procedure as for (+)-**10**, from (−)-**7** (0.50 g, 2.0 mmol) to give (−)-**11** (0.67 g, 97%, >99% ee) as a white solid; TLC R_f was concentration dependent; $[\alpha]_D^{20} = -45$ (*c* 0.55, $CHCl_3$); mp 115–117 °C; IR (KBr) 3296, 3273, 3049 cm^{-1}; ^1H NMR (400 MHz, pyridine-d_5) δ 1.52 (1H, dm, *J* = 10.1 Hz), 1.76 (1H, dm, *J* = 10.1 Hz), 1.97–2.04 (1H, m), 2.22 (1H, dd_{AB}, J_{AB} = 13.2, 4.6 Hz), 2.38 (1H, m), 2.46 (1H, dt, *J* = 12.7, 3.6 Hz), 2.88 (1H, dd_{AB}, J_{AB} = 13.2, 3.1 Hz), 3.03 (1H, d, *J* = 4.3 Hz), 3.28–3.33 (1H, m), 3.85 (1H, d_{AB}, J_{AB} = 13.3 Hz), 3.96 (1H, d_{AB}, J_{AB} = 13.3 Hz), 6.65 (1H, br s), 7.30–7.33 (1H, m), 7.38–7.47 (3H, m), 7.49–7.61 (5H, m), 7.84 (1H, d, *J* = 8.1 Hz), 7.95–7.97 (1H, m), 7.95–7.97 (1H, m), 9.21 (1H, d, *J* = 8.6 Hz); ^{13}C NMR (100 MHz, pyridine-d_5) δ 31.4, 39.1, 40.8, 41.3, 47.7, 53.1, 59.2, 80.3, 122.4, 125.5, 125.6, 126.0, 127.5, 128.4, 129.1, 129.5, 129.8, 132.8, 136.3, 142.4, 146.2; HRMS (FAB+) [M+H]: calcd for $C_{24}H_{26}ON$: 344.2014, found: 344.2013. Anal. Calcd for $C_{24}H_{25}NO$: C, 83.93; H, 7.34. Found: C, 84.06; H, 7.39.

4.14. (1*R*,2*R*,4*R*,5*R*)-5-(*N*-Benzyl-*N*-ethyl-amino)-2-phenyl-bicyclo[2.2.1]heptan-2-ol (+)-14

EtBr (0.25 mL, 3.4 mmol) and Hünig's base (89 μL, 0.51 mmol) were added to a solution of (+)-**10** (0.10 g, 0.34 mmol) in CH_3CN (5 mL). The mixture was heated to 80 °C in a capped vial (Pyrex) overnight. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (SiO_2, heptane–EtOAc, 3:7) to give (+)-**14** as a clear oil (0.10 g, 93%) of >99% ee; TLC R_f was concentration dependent; $[\alpha]_D^{20} = +20$ (*c* 3.0, $CHCl_3$); IR (NaCl) 3413 (br) cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.74 (3H, t, *J* = 7.2 Hz), 1.31–1.34 (1H, m), 1.36–1.43 (1H, m), 1.64–1.68 (1H, m), 2.00 (1H, dd_{AB}, *J* = 13.2, 3.6 Hz), 2.12–2.14 (1H, m), 2.17–2.23 (2H, m), 2.41–2.46 (2H, m), 2.51–2.58 (1H, m), 2.70–2.74 (1H, m), 3.47 (2H, s), 3.56 (1H, s), 7.09–7.18 (1H, m), 7.18–7.22 (2H, m) 7.25–7.30 (2H, m), 7.36–7.38 (2H, m), 7.68–7.71 (2H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 8.9, 30.8, 40.1, 41.8, 43.1, 44.7, 49.9, 55.9, 61.4, 79.4, 126.4, 127.0, 127.6, 129.0, 129.5, 140.3, 149.9 (one peak hidden by solvent); HRMS (FAB^+) [M+H]: calcd for $C_{22}H_{28}NO$: 322.2171, found: 322.2180. Anal. Calcd for $C_{22}H_{27}NO$: C, 82.20; H, 8.47; N, 4.36. Found: C, 82.19; H, 8.52; N, 4.39.

4.15. (1*S*,2*R*,4*S*,5*S*)-2-Benzyl-5-(*N*-benzyl-*N*-ethyl-amino)-bicyclo[2.2.1]heptan-2-ol (−)-17

The title compound was synthesized following the same procedure as for (+)-**14**, from (−)-**13** (0.11 g, 0.35 mmol) to give (−)-**17** (82%, 0.096 g, 98% ee) as a yellow oil; TLC R_f was concentration dependent; $[\alpha]_D^{20} = -21$ (*c* 1.3, $CHCl_3$); IR (NaCl) 3433 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.68 (3H, t, *J* = 7.2 Hz), 1.25–1.33 (2H, m), 1.40–1.43 (1H, m), 1.48–1.53 (1H, m), 1.67–1.71 (1H, m), 1.90 (1H, dt, *J* = 12.8, 3.2 Hz), 2.04–2.05 (2H, m), 2.29–2.34 (1H, m), 2.43–2.48 (1H, m), 2.64–2.67 (1H, m), 2.75 (1H, d_{AB}, J_{AB} = 13.6 Hz), 2.78 (1H, br s), 2.93 (1H, d_{AB}, J_{AB} = 13.2 Hz), 3.38 (1H, d_{AB}, J_{AB} = 14.4 Hz), 3.42 (1H, d_{AB}, J_{AB} = 14.0 Hz), 7.05–7.09 (1H, m), 7.11–7.14 (3H, m) 7.21–7.25 (2H, m), 7.27–7.29 (2H, m), 7.43–7.45 (2H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 8.8, 30.2, 39.2, 40.2, 41.7, 44.7, 47.9, 48.0, 55.9, 61.5, 78.8. 126.8, 127.4, 128.5, 128.9, 129.3, 131.6, 139.2, 140.5; HRMS (FAB^+) [M+H]: calcd for $C_{23}H_{30}NO$: 336.2327, found: 336.2330. Anal. Calcd for $C_{23}H_{29}NO$: C, 82.34; H, 8.71; N, 4.18. Found: C, 83.30; H, 8.67; N, 4.14.

4.16. (1*S*,2*S*,4*S*,5*S*)-5-(*N*-Benzyl-*N*-ethyl-amino)-2-(2-methoxy-phenyl)-bicyclo[2.2.1]heptan-2-ol ((+)-16)

The title compound was synthesized following the same procedure as for (+)-**14**, from (−)-**12** (0.10 g, 0.31 mmol) to give (+)-**16** (0.094 g, 86%, 99% ee) as a clear oil; TLC R_f was concentration dependent; $[\alpha]_D^{20} = +21$ (*c* 2.5, $CHCl_3$); IR (NaCl) 3554 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.87 (3H, t, *J* = 7.2 Hz), 1.35–1.39 (1H, m), 1.61–1.64 (1H, m), 1.66–1.70 (1H, m), 2.06 (1H, dd_{AB}, *J* = 13.2, 4.4 Hz), 2.19–2.21 (1H, m), 2.59–2.79 (5H, m), 2.86–2.91 (1H, m), 3.09 (3H, s), 3.56 (1H, d_{AB}, J_{AB} = 14.0 Hz), 3.78 (1H, d_{AB}, J_{AB} = 14.0 Hz), 4.10 (1H, s), 6.50 (1H, dd, *J* = 8.0, 0.8 Hz), 6.85–6.89 (1H, m) 7.03–7.08 (1H, m), 7.11–7.18 (1H, m), 7.22–7.29 (3H, m), 7.59–7.61 (2H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 8.9, 28.6, 38.1, 38.4, 41.3, 45.0, 46.7, 54.9, 56.2, 64.2, 80.6, 112.0, 121.0, 126.3, 127.2, 128.8, 129.6, 137.4, 141.6, 157.9, (one peak hidden by solvent); HRMS (FAB^+) [M+H]: calcd for $C_{23}H_{30}NO_2$: 352.2277, found: 352.2272. Anal. Calcd for $C_{23}H_{29}O_2N$: C, 78.59; H, 8.32; N, 3.99. Found: C, 78.45; H, 8.27; N, 4.06.

4.17. (1*S*,2*S*,4*S*,5*S*)-5-(*N*-Benzyl-*N*-ethyl-amino)-2-(1-naphthyl)-bicyclo[2.2.1]heptan-2-ol (−)-15

The title compound was synthesized following the same procedure as for (+)-**14**, from (−)-**11** (0.10 g, 0.29 mmol) to give (−)-**15** (0.076 g, 70%, >99% ee) as a yellow oil; TLC R_f was concentration dependent; $[\alpha]_D^{20} = -1.5$ (*c* 1.4, $CHCl_3$); IR (NaCl) 3355 (br) cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.80 (3H, t, J = 7.2 Hz), 1.34–1.38 (1H, m), 1.51–1.60 (2H, m), 2.09–2.10 (1H, m), 2.12–2.16 (1H, m), 2.25 (1H, br s), 2.30 (1H, dt, J = 12.4, 3.6 Hz), 2.46–2.55 (1H, m), 2.59–2.68 (1H, m), 2.72–2.76 (2H, m), 2.78–2.82 (1H, m), 3.51 (1H, d_{AB}, J_{AB} = 14.0 Hz), 3.64 (1H, d_{AB}, J_{AB} = 14.0 Hz), 7.10–7.14 (1H, m) 7.20–7.26 (3H, m), 7.28–7.32 (1H, m), 7.35–7.41 (2H, m), 7.49–7.64 (2H, m), 7.62–7.64 (1H, m), 7.71–7.73 (1H, m), 8.97–8.99 (1H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 8.9, 29.3, 38.8, 40.9, 41.5, 44.8, 47.8, 56.0, 62.9, 81.1, 122.5, 125.0, 125.8, 126.0, 127.4, 128.7, 128.8, 128.9, 129.3, 129.5, 132.7, 136.3, 141.0, 144.3; HRMS (FAB^+) [M+H]: calcd for $C_{26}H_{30}NO$: 372.2327, found: 372.2333. Anal. Calcd for $C_{26}H_{29}NO$: C, 84.06; H, 7.87, N, 3.77. Found: C, 84.15; H, 7.83; N, 3.73.

4.18. (1*R*,2*R*,4*S*,6*S*)-6-(*N*-Benzyl-*N*-ethyl-amino)-2-phenyl-bicyclo[2.2.2]octan-2-ol (+)-37

The title compound was synthesized following the same procedure as for (+)-**14**, from (+)-**36** (0.28 g, 0.91 mmol), except that the reaction time was 3 days. The crude product was purified by column chromatography (SiO_2, heptane–EtOAc, 8:2) to give (+)-**37** (0.22 g, 70%, 99% ee) as a yellow oil; TLC R_f was concentration dependent. IR (KBr) 3179 (br) cm^{-1}; $[\alpha]_D^{20} = +165$ (*c* 0.6, $CHCl_3$); ^1H NMR (C_6D_6, 400 MHz) δ 0.64 (3H, t, J = 7.2 Hz), 0.93–1.02 (1H, m), 1.14–1.24 (1H, m), 1.26–1.35 (1H, m), 1.48–1.58 (1H, m), 1.60–1.64 (1H, m), 1.76–1.84 (2H, m), 1.99–2.03 (1H, m), 2.18 (1H, dt, J = 14.4, 3.2 Hz), 2.34 (1H, dt, J = 14.4, 2.0 Hz), 2.53–2.64 (2H, m), 2.71–2.80 (1H, m), 3.40–3.57 (2H, m), 7.07–7.12 (1H, m), 7.15–7.19 (3H, m), 7.29–7.35 (4H, m), 7.78–7.81 (2H, m), 8.12 (1H, br s); ^{13}C NMR (C_6D_6, 100 MHz) δ 7.8, 21.8, 23.9, 27.1, 33.6, 37.6, 42.0, 43.9, 53.8, 59.4, 76.1, 126.9, 127.5, 127.7, 128.7, 129.2, 129.4, 139.9, 149.5. HRMS (FAB^+) [M]: calcd for $C_{23}H_{29}NO$: 335.2249, found: 335.2248. Anal. Calcd for $C_{23}H_{29}NO$: C, 82.34; H, 8.71, N, 4.18. Found: C, 82.29; H, 8.77; N, 4.14.

4.19. (1*S*,2*R*,4*R*)-2-Acetoxy-6-oxo-2-phenyl-bicyclo- [2.2.2]-octane (−)-27

Ac_2O (0.63 mL, 6.7 mmol) and DMAP (cat.) were added to a solution of (+)-**23** (0.50 g, 2.3 mmol) in pyridine (10 mL). The reaction mixture was stirred at 60 °C for 2 d then satd aqueous $NaHCO_3$ was added and the aqueous phase was extracted with diethyl ether (3 × 30 mL). The combined organic phases were washed repeatedly with $CuSO_4$ solution until there was no color change of the aqueous phase, then washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the remaining crude product was purified by column chromatography to give (−)-**27** (0.43 g, 72%, 99% ee) as white crystals; TLC R_f 0.53 (heptane–EtOAc, 1:1); mp 118–120 °C, $[\alpha]_D^{20} = -48$ (*c* 0.4, $CHCl_3$); IR (KBr) 1738, 1725 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.93–1.00 (1H, m), 1.02–1.07 (1H, m), 1.15–1.20 (2H, m), 1.53 (3H, s), 1.70–1.73 (1H, m), 1.94 (1H, dt, J = 18.4, 2.8 Hz), 2.08 (1H, dt, J = 16.0, 2.8 Hz), 2.15 (1H, dt, J = 18.8, 2.8 Hz), 2.43 (1H, dt, J = 16.0, 2.8 Hz), 2.89 (1H, t, J = 2.8 Hz), 7.02–7.06 (1H, m), 7.10–7.15 (2H, m), 7.24–7.27 (2H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 18.5, 21.8, 23.9, 28.8, 38.6, 43.8, 54.1, 83.9, 126.2, 127.9, 128.8, 142.6, 168.4, 210.2; HRMS (FAB+) [M+Na]: calcd for $C_{16}H_{18}O_3Na$: 281.1154, found: 281.1141. Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.30; H, 6.96.

4.20. (1*S*,2*R*,4*R*)-2-Acetoxy-6-oxo-2-(1-naphthyl)-bicyclo-[2.2.2]octane (−)-28

The title compound was synthesized following the same procedure as for (−)-**27**, from (+)-**24** (0.42 g, 1.6 mmol), except that the reaction time was 1.5 days. The crude product was purified by column chromatography (SiO_2, pentane–diethyl ether, 1:1) to give (−)-**28** (0.32 g, 65%, 99% ee) as white crystals; TLC R_f 0.33 (pentane–diethyl ether, 1:1); mp 188–190 °C; $[\alpha]_D^{20} = -28$ (*c* 0.6, $CHCl_3$); IR (KBr) 1734 cm^{-1}; ^1H NMR (400MHz, C_6D_6, mixture of two rotamers); δ 0.82–1.08 (br m), 1.09–1.23 (br m), 1.41–1.61 (br m), 1.62–1.70 (br m), 1.99 (dt, J = 18.4, 2.8 Hz), 2.01–2.09 (br d), 2.22–2.39 (1H, br m), 2.24 (br d, J = 13.6 Hz), 3.00 (br d, J = 15.2 Hz), 3.40 (br s), 4.33 (br s), the reported peaks integrates to 13H in total, 7.19–7.36 (4H, m), 7.39–7.51 (1H, m), 7.54 (1H, d, J = 8.4 Hz), 7.59–7.70 (1H, m), 8.36 (br d, J = 7.6 Hz), 8.76–8.83 (br m), the last two peaks integrate 1H together; ^{13}C NMR is not given since the two rotamers give peaks that are too broad; HRMS (FAB^+) [M+Na]: calcd for $C_{20}H_{20}O_3Na$: 331.1310, found: 331.1320. Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 77.84; H, 6.60.

4.21. (1*S*,2*R*,4*R*)-2-Acetoxy-6-oxo-2-(2-methoxy-phenyl)-bicyclo[2.2.2]octane (+)-29

The title compound was synthesized following the same procedure as for (−)-**27**, from (−)-**25** (0.42 g, 1.6 mmol), except that the reaction time was 4.5 days (another portion of 3 equiv Ac_2O and DMAP (cat.) was added after 3.5 days). The crude product was purified by column chromatography (SiO_2, heptane–EtOAc, 8:2) to give (+)-**29** (0.15 g, 52%, 99% ee) as white crystals; TLC R_f 0.43 (heptane–EtOAc, 1:1); mp 152–155 °C; $[\alpha]_D^{20} = +24$ (*c* 0.25, $CHCl_3$); IR (KBr) 1725 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 1.00–1.12 (2H, m), 1.36–1.47 (1H, m), 1.47–1.54 (1H, m), 1.62 (3H, s), 1.77–1.80 (1H, m), 2.00 (1H, dt, J = 18.4, 3.2 Hz), 2.34 (1H, dt, J = 15.2, 2.4 Hz), 2.34 (1H, dt, J = 18.4, 2.8 Hz), 2.53 (1H, dt, J = 15.6, 3.2 Hz), 3.26 (3H, s), 3.84–3.85 (1H, m), 6.54 (1H, dd, J = 8.4, 1.2 Hz), 6.83 (1H, td, J = 7.6, 1.2 Hz), 7.04–7.08 (1H, m), 7.32 (1H, dd, J = 8.0, 1.6 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 19.4, 21.8, 24.8, 28.6, 40.9, 43.9, 49.9, 55.3, 83.6, 112.8, 120.5, 129.3, 129.3, 129.4, 158.4, 168.6, 210.9; HRMS (FAB^+) [M+Na]: calcd for $C_{17}H_{20}O_4Na$: 311.1259, found: 311.1244. Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.76; H, 6.94. *6-(2-Methoxy-phenyl)-bicyclo[2.2.2]oct-5-en-2-one* was isolated as a by-product (29%); TLC R_f 0.71 (heptane–EtOAc, 1:1); ^1H NMR (400 MHz, C_6D_6) δ 1.27–1.32 (2H, m), 1.59–1.69 (2H, m), 1.81 (1H, dd, J = 18.0, 2.4 Hz), 1.98 (1H, dm, J = 18.0 Hz), 2.50 (1H, h, J = 2.8 Hz), 3.27 (3H, s), 3.68–3.70 (1H, m), 6.26 (1H, dd, J = 6.4, 1.6 Hz), 6.47–6.49 (1H, dd, J = 8.4, 1.2 Hz), 6.82 (1H, td, J = 7.2, 1.2 Hz), 7.04–7.08 (1H, m), 7.11–7.13 (1H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 23.0, 25.4, 33.2, 41.1, 53.6, 55.1, 111.4, 121.2, 129.0, 129.3, 129.8, 133.0, 141.3, 157.7, 210.4; HRMS (FAB^+) [M+H]: calcd for $C_{15}H_{16}O_2$: 228.1150, found: 228.1150.

4.22. (1*S*,2*S*,4*R*)-2-Acetoxy-6-oxo-2-benzyl-bicyclo[2.2.2]octane (+)-30

The title compound was synthesized following the same procedure as for (−)-**27**, from (+)-**26** (2.05 g, 8.9 mmol), except that the reaction was heated at 60 °C for 4 days (another portion of 3 equiv Ac_2O and DMAP (cat.) was added after 3 days), then at 80 °C for another 3 days. The crude product was purified by column chromatography (SiO_2, heptane–EtOAc, 75:25) to give (+)-**30** (1.13 g, 47%, 99% ee) as white crystals; TLC R_f 0.57 (heptane–EtOAc, 1:1); mp 132–133 °C; $[\alpha]_D^{20} = +51$ (*c* 0.8, $CHCl_3$); IR (KBr) 1727 cm^{-1};

^{1}H NMR (400 MHz, C_6D_6) δ 1.00–1.05 (2H, m), 1.28–1.36 (1H, m), 1.41–1.51 (1H, m), 1.52–1.57 (1H, m), 1.55 (3H, s), 1.58–1.62 (1H, m), 1.88 (1H, dt, J = 18.4, 3.2 Hz), 1.98 (1H, m), 2.02 (1H, m), 2.93 (1H, t, J = 3.2 Hz), 3.06 (1H, d_{AB}, J_{AB} = 14.4 Hz), 3.47 (1H, d_{AB}, J_{AB} = 14.4 Hz), 7.05–7.15 (5H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 19.1, 22.3, 24.5, 28.6, 40.5, 40,7, 43.5, 49.9, 84.8, 127.4, 128.9, 130.7, 136.8, 170.3, 210.1; HRMS (FAB$^+$) [M+Na]: calcd for $C_{17}H_{20}O_3Na$: 295.1310, found: 295.1318. Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.08; H, 7.33.

4.23. (1*R*,2*R*,4*S*,6*S*)-6-Benzylamino-2-phenyl-bicyclo-[2.2.2]octan-2-ol (+)-36

Benzylamine (0.70 mL, 6.8 mmol), acetic acid (0.15 mL, 2.6 mmol) and MS 4 Å were added to a solution of (−)-**27** (0.33 g, 1.3 mmol) in toluene (15 mL), and the mixture was heated to 80 °C for 2 days. The MS were filtered off and the toluene was removed under reduced pressure. The remaining mixture was dissolved in methanol (20 mL) and cooled to 0 °C, then $NaBH_4$ (0.49 g, 13 mmol) was added. The mixture was stirred for 15 min then water was added and the aqueous phase was extracted with diethyl ether (3 × 40 mL). The combined organic phases were washed with satd aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4. The solvent was removed under reduced pressure and the remaining mixture was dissolved in dry THF. The mixture was cooled to 0 °C then a 1 M solution of $LiAlH_4$ in THF (5.2 mL, 5.2 mmol) was added. The cooling bath was removed and the mixture was stirred at rt for 40 min. The reaction was quenched by the addition of water (0.2 mL), 15% NaOH-solution (0.2 mL) and water (0.6 mL), and after 20 min of stirring at rt the precipitate was filtered off and rinsed with diethyl ether. The solvents were removed under reduced pressure, and the crude product was purified by column chromatography (SiO_2, heptane–EtOAc, 60:40 + 0.3% NEt_3) giving (+)-**36** as yellow crystals (0.36 g, 91%, 99% ee) that were pure according to NMR analysis. The product was recrystallized from heptane–EtOAc to give white crystals; TLC R_f concentration dependent; mp 118–119 °C; $[\alpha]_D^{20} = +129$ (c 1.2, $CHCl_3$); IR (KBr) 3263, 3146; ^{1}H NMR(400 MHz, C_6D_6) δ 0.87–0.95 (1H, m), 1.07–1.16 (1H, m), 1.24–1.32 (2H, m), 1.39–1.47 (1H, m), 1.58–1.66 (2H, m), 1.73–1.76 (1H, m), 2.17 (1H, dt, J = 14.4, 3.2 Hz), 2.42 (1H, dt, J = 14.4, 2.4 Hz), 2.61–2.66 (1H, m), 3.37 (1H, d_{AB}, J_{AB} = 13.2 Hz), 3.57 (1H, d_{AB}, J_{AB} = 13.2 Hz), 7.07–7.13 (1H, m), 7.13–7.21 (7H, m), 7.31–7.36 (2H, m), 8.25 (1H, br s); ^{13}C NMR (100 MHz, C_6D_6) δ 21.7, 24.0, 26.8, 34.9, 39.2, 44.1, 51.6, 57.0, 76.0, 126.9, 127.6, 127.8, 128.3, 128.9, 129.1, 140.2, 149.6; HRMS (FAB+) [M+Na]: calcd for $C_{21}H_{25}NONa$: 330.1834, found: 330.1836. Anal. Calcd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 81.97; H, 8.22, N, 4.53.

4.24. (1*R*,2*R*,4*S*,6*S*)-6-Benzylamino-2-(1-naphthyl)-bicyclo-[2.2.2]octan-2-ol (+)-41

The title compound was synthesized following the same procedure as for (+)-**36**, from (−)-**28** (0.25 g, 0.81 mmol). The crude product was purified by column chromatography (SiO_2, heptane–EtOAc, 7:3 + 0.3% NEt_3) to give (+)-**41** (0.16 g, 57%, 99% ee) as a yellow solid; TLC R_f concentration dependent; mp 119–125 °C; $[\alpha]_D^{20} = +13$ (c 0.45, $CHCl_3$); IR(KBr) 3288, 3191 (br) cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 1.07–1.24 (3H, m), 1.44–1.48 (1H, m), 1.61–1.75 (3H, m), 2.18–2.22 (1H, m), 2.42 (1H, m), 2.69–2.76 (2H, m), 3.42 (1H, d_{AB}, J_{AB} = 13.2 Hz), 3.62 (1H, d_{AB}, J_{AB} = 12.8 Hz), 7.05–7.11 (2H, m), 7.13–7.16 (4H, m), 7.29–7.35 (2H, m), 7.38–7.40 (1H, m), 7.44–7.48 (1H, m), 7.65–7.67 (1H, m), 7.74–7.76 (1H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 22.8, 24.3, 26.9, 34.4, 35.9, 46.7, 51.5, 56.9, 77.5, 122.8, 124.8, 125.3, 125.7, 127.8, 128.5, 128.9, 129.1, 129.5, 130.1, 133.4, 136.5, 140.2, 144.8; HRMS (FAB$^+$) [M+H]: calcd for $C_{25}H_{28}ON$: 358.2171, found: 358.2173. Anal. Calcd for $C_{25}H_{27}ON$: C, 83.99; H, 7.61; N, 3.92. Found: C, 83.90; H, 7.56; N, 3.90. (1*R*,2*R*,4*S*,6*S*)-6-(*N*-Benzyl-*N*-ethyl-amino)-2-(1-naphthyl)-bicyclo[2.2.2]octan-2-ol (**43**) was isolated as a by-product in 21% yield; TLC R_f concentration dependent;^{1}H NMR (400 MHz, C_6D_6) δ 0.68 (3H, t, J = 7.0 Hz), 1.13–1.38 (4H, m), 1.68–1.70 (1H, m), 1.70–1.78 (1H, m), 1.80–1.89 (1H, m), 1.90–2.02 (2H, m), 2.60–2.75 (3H, m), 2.81–2.90 (2H, m), 3.55 (2H, br, s) 7.03–7.11 (3H, m), 7.27–7.40 (5H, m), 7.41–7.47 (1H, m), 7.64 (1H, d, J = 8.0 Hz), 7.74 (1H, dd, J = 8.0, 1.6 Hz), 9.40 (1H, d, J = 8.8 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 8.0, 23.1, 24.2, 27.3, 33.1, 33.8, 42.0, 47.0, 53.8, 59.4, 77.2, 122.1, 124.9, 125.4, 125.8, 127.7, 128.9, 129.0, 129.1, 129.3, 130.2, 133.3, 136.4, 139.7, 145.1; HRMS (FAB$^+$) [M+H]: calcd for $C_{27}H_{32}ON$: 386.2484, found: 386.2479.

4.25. (1*R*,2*S*,4*S*,6*S*)-6-Benzylamino-2-benzyl-bicyclo[2.2.2]octan-2-ol (+)-42

The title compound was synthesized following the same procedure as for (−)-**27**, from (+)-**30** (0.75 g, 2.8 mmol). The crude product was purified by column chromatography (SiO_2, heptane–EtOAc, 9:1→7:3) to give (+)-**42** (0.21 g, 23%, 99% ee) as a yellow solid; TLC R_f concentration dependent; mp 78–83 °C; $[\alpha]_D^{20} = +88$ (c 0.65, $CHCl_3$); IR (KBr) 3267 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.98–1.27 (5H, m), 1.41–1.43 (1H, m), 1.49–1.65 (4H, m), 1.94–2.01 (1H, m), 2.48–2.52 (1H, m), 2.66 (1H, d_{AB}, J_{AB} = 13.6 Hz), 3.07 (1H, d_{AB}, J_{AB} = 12.8 Hz), 3.18 (1H, d_{AB}, J_{AB} = 12.8 Hz), 3.31 (1H, d_{AB}, J_{AB} = 12.8 Hz), 6.97–7.00 (2H, m), 7.03–7.15 (4H, m), 7.24–7.29 (2H, m), 7.61–7.64 (2H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 22.0, 24.4, 26.7, 34.6, 34.8, 46.5, 48.7, 51.2, 56.4, 74.3, 126.6, 127.6, 128.2, 128.8, 129.0, 131.7, 139.9, 140.2; HRMS (FAB$^+$) [M+H]: calcd for $C_{22}H_{28}ON$: 322.2171, found: 322.2166. Anal. Calcd for $C_{22}H_{27}ON$: C, 82.20; H, 8.47; N, 4.36. Found: C, 82.15; H, 8.43; N, 4.51.

4.26. (1*R*,2*S*,4*S*,6*S*)-6-(*N*-Benzyl-*N*-ethyl-amino)-2-benzyl-bicyclo[2.2.2]octan-2-ol (+)-44

Compound **44** was isolated as byproduct (0.18 g, 18%) (clear oil); TLC R_f concentration dependent; $[\alpha]_D^{20} = +170$ (c 0.5, $CHCl_3$); IR (KBr) 3224 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.50 (3H, t, J = 6.8 Hz), 1.12–1.30 (4H, m), 1.48–1.53 (1H, m), 1.53–1.73 (4H, m), 1.85 (1H, br s), 1.99 (1H, dm, J = 13.2 Hz), 2.35–2.47 (3H, m), 2.66 (1H, d_{AB}, J_{AB} = 13.2 Hz), 3.06 (1H, d_{AB}, J_{AB} = 13.6 Hz), 3.10–3.40 (2H, m), 7.03–7.26 (8H, m), 7.56–7.60 (2H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 7.9, 22.3, 24.3, 27.0, 32.5, 33.4, 41.8, 45.9, 48.1, 53.6, 59.0, 74.5, 126.6, 127.6, 128.2, 129.0, 129.5, 131.7, 139.7, 139.8; HRMS (FAB$^+$) [M+H]: calcd for $C_{24}H_{32}ON$: 350.2484, found: 350.2477. Anal. Calcd for $C_{24}H_{31}ON$: C, 82.47; H, 8.94; N, 4.01. Found: C, 82.40; H, 8.97; N, 3.96.

4.27. (1*S*,2*R*,3*S*)-3,6-Dibenzyl-5-methyl-4-oxa-6-aza-tricyclo-[5.3.1.0^{3,8}]undecane (+)-45

Compound **45** was also isolated as a byproduct (0.19 g, 19%) (clear oil); TLC R_f 0.78 (heptane–EtOAc, 1:1); $[\alpha]_D^{20} = +4$ (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 0.76–0.87 (1H, m), 1.05–1.10 (2H, m), 1.27 (3H, d, J = 5.6 Hz), 1.28–1.35 (2H, m), 1.49–1.63 (3H, m), 1.68–1.70 (1H, m), 1.77 (1H, dm, J = 14.8 Hz), 2.67 (1H, d_{AB}, J_{AB} = 13.6 Hz), 2.68–2.73 (1H, m), 2.83 (1H, d_{AB}, J_{AB} = 14.0 Hz), 3.47 (1H, d_{AB}, J_{AB} = 14.4 Hz), 3.71 (1H, d_{AB}, J_{AB} = 14.4 Hz), 4.69 (1H, q, J = 5.6 Hz), 7.07–7.10 (1H, m), 7.14–7.21 (3H, m), 7.23–7.30 (4H, m), 7.46–7.48 (2H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 20.6, 20.7, 26.1, 26.7, 29.4, 29.9, 38.4, 47.6, 50.2, 52.9, 75.3, 77.0, 126.7, 127.2, 128.3, 128.8, 129.0, 131.7, 138.9, 141.4; HRMS (FAB$^+$) [M+Na]: calcd for $C_{24}H_{29}ONNa$: 370.2143, found:

370.2143. Anal. Calcd for $C_{24}H_{29}ON$: C, 82.95; H, 8.41; N, 4.03. Found: C, 83.06; H, 8.37; N, 4.04.

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