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# Stereoselective synthesis of pinane-type tridentate aminodiols and their application in the enantioselective addition of diethylzinc to benzaldehyde

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ABSTRACT

A library of pinane-based aminodiols were prepared from commercially available (1*R*)-(−)-myrtenol (−)-**1**. Compound (−)-**1** was transformed into allyl trichloroacetamide (+)-**2** via the acetimidate, followed by the Overman rearrangement. In order obtain the aminodiol structure, (+)-**2** was subjected to stereoselective dihydroxylation with $OsO_4$, resulting in dihydroxy trichloroacetamide (+)-**3**. The trichloroacetyl group was removed from (+)-**3** with aqueous HCl, and the (1*R*,2*R*,3*S*,5*R*)-3-amino-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-ol hydrochloride (−)-**4** obtained was transformed to primary, secondary and tertiary aminodiols by reductive amination, N-alkylation of aminodiol (+)-**9** and debenzylation of *N*-benzyl aminodiol (+)-**10**, respectively. In the reactions of (+)-**9** and (+)-**14** with formaldehyde, highly regioselective ring closure was observed. In contrast with earlier results, the aminodiols gave pinane-fused oxazolidines (+)-**11** and (−)-**15**. The aminodiols and their oxazolidine derivatives **5**–**15** were applied as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde. The best enantioselectivity was observed in the case of the *N*-benzyl-substituted derivative (+)-**9**.



## 1. Introduction

In recent years, aliphatic aminodiols bearing a 1,2- and a 1,3-aminoalcohol moiety in the same molecule have proven to be useful building blocks. They have been applied as chiral catalysts or starting materials in the stereoselective synthesis of compounds of pharmacological interest. In addition to their synthetic importance, aminodiols can also be applied as chiral ligands and auxiliaries in enantioselective transformations.[1–9] The asymmetric addition of diethylzinc to aldehydes has become a highly investigated model reaction, with the application of chiral promoters such as 1,2- and 1,3-difunctionalized ligands.[5–9]

Amino alcohols, and especially β-amino alcohols, have proven to be excellent ligands for the addition mentioned above.[10–12] Since the report by Oguni and Omi in 1984,[13] a great number of β-amino alcohols have been investigated.[4,14,15] The first very high enantioselectivity in the addition of diethylzinc was achieved by Noyori et al., who used DAIB, a terpene-based chiral ligand.[16] Several natural chiral terpenes, including (+)-pulegone,[17] α- and β-pinene[18,19] and fenchone-camphor,[20] have also proven to be excellent sources for the synthesis of various amino alcohols, which were successfully applied in enantioselective syntheses. The transformation of enantiomerically pure α-pinene into β-amino acid derivatives such as 1,3-aminoalcohols was recently reported. These synthons served as chiral auxiliaries in the enantioselective synthesis of secondary alcohols.[21–23]

Many naturally occurring molecules containing an aminodiol function exhibit a marked biological activity: myriocin, isolated from *M. albomyces*, is known to be a potent immunostimulator, while swainsonin, an acyclic aminodiol, is an inhibitor of glycoprotein processing.[24] Some compounds containing an aminodiol moiety have proven to be potential HIV protease inhibitors,[25] while others exert renin-inhibitory activity.[26,27] Aminodiols are also useful starting materials for the synthesis of biologically active natural compounds, for example, (−)-cytoxazone, a selective modulator of the secretion of $T_H2$ cytokine, a microbial metabolite isolated from cultures of Streptomyces species.[28]

Pinane- and carane-based 3-amino-1,2-diols are known to be excellent building blocks for the synthesis of 1,3-oxazines and oxazolidines. The formation of these noteworthy heterocyclic systems depends upon which hydroxy groups participate in the ring-closure process. Different types of monoterpene-based aminodiols have already been examined in order to investigate the tendencies of monoterpene-based aminodiols to furnish either the spirooxazolidine or the 1,3-oxazine ring system.[21,22,29–31]

Our aim herein was to synthetize new chiral pinane-based aminodiols and their ring-closed derivatives from readily available (1*R*)-(−)-myrtenol and to apply them in the enantioselective synthesis of 1-phenyl-1-propanol.

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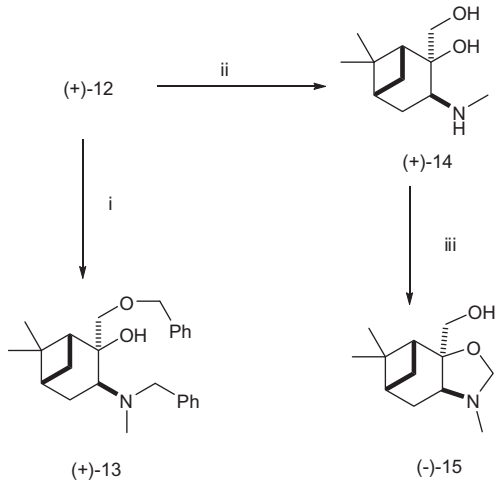
## 2. Results and discussion

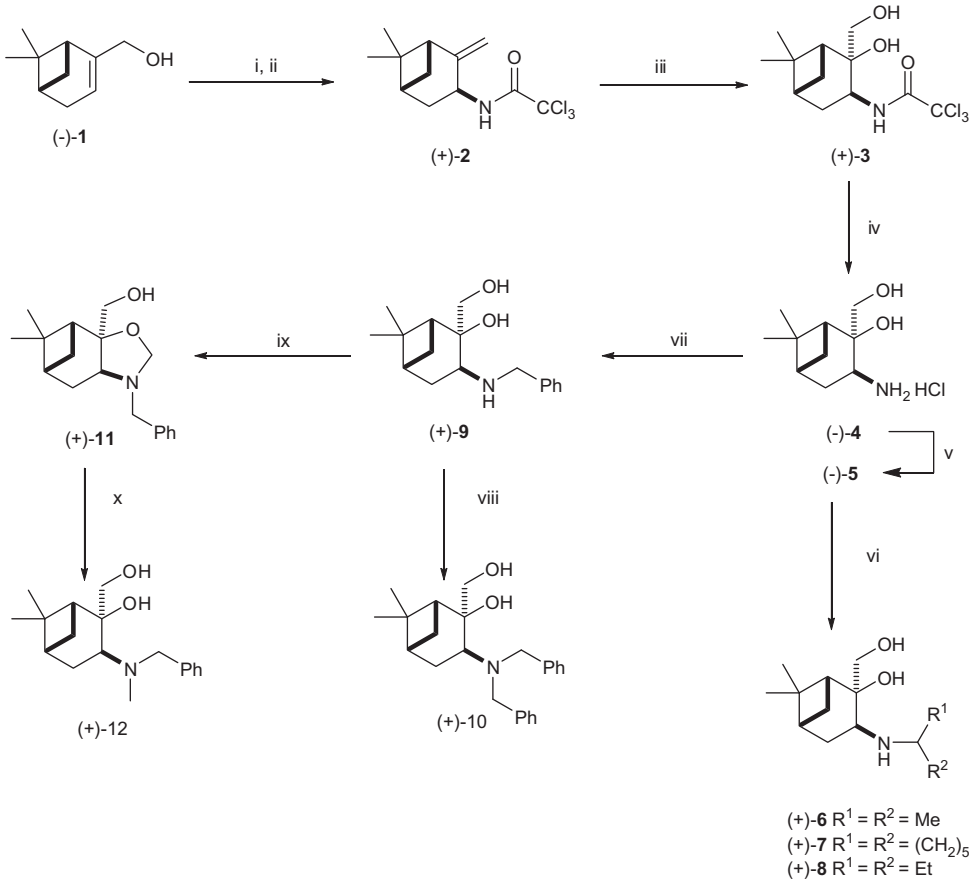
### 2.1. Syntheses of pinane-based aminodiols

The synthetic routes developed for aminodiols **5**–**15** are presented in Schemes 1 and 2. As reported in the literature,[32,35,36] commercially available (1*R*)-myrtenol (−)-**1** was transformed into allyl trichloroacetimidate, which was followed by an Overman rearrangement in the presence of $K_2CO_3$, resulting in allyl trichloroacetamide (+)-**2**. In order to build up the aminodiol structure, the exocyclic olefin function was dihydroxylated with $KMnO_4$. Despite the good stereoselectivity of the reaction, the product was isolated in only 10% yield with recovery of the unreacted starting material. When $OsO_4$/NMO was applied instead of $KMnO_4$, the desired aminodiol derivative (+)-**3** was obtained in an 83% yield (Scheme 1). Our NMR studies on the crude product proved that, probably because of the sterically hindered rigid backbone of the monoterpene, the reaction was highly stereoselective: only diastereomer (+)-**3** was detected and isolated.[37,38] The stereochemistry was established by NOESY.

Several methods are already known for removal of the trichloroacetyl group.[39–41] We found it best to use an 18% aqueous HCl solution for this cleavage at room temperature, with stirring for 24 h (Scheme 1). Primary aminodiol (−)-**5** was transformed into secondary ones **6**, **7** and **8** by reductive amination, (−)-**5** was stirred with different ketones, such as acetone, cyclohexanone and diethyl ketone, and the Schiff base formed in situ was reduced with $NaBH_4$. Starting from (−)-**4**, additional secondary and tertiary aminodiols were prepared. A bulky group was conveniently introduced onto the amino moiety by the reaction of (−)-**4** with benzaldehyde in the presence of $Et_3N$ and $NaBH_4$. In order to increase the steric hindrance on the nitrogen, an additional benzyl group




**Scheme 2.** Reagents and conditions: (i) 1.08 equiv BnBr, NaH, THF, reflux, 8 h; yield: 44%; (ii) Pd(C) 5%, $H_2$, 1 atm, MeOH, rt, 2 h; yield: 57%; (iii) 35% HCHO/$H_2O$, $Et_2O$, rt, 1 h, yield: 41%.




**Scheme 1.** Reagents and conditions: (i) 1.8 equiv $CCl_3CN$, 1.5 equiv DBU, DCM, 0 °C; (ii) anhydrous $K_2CO_3$, dry xylene, reflux, 24 h, yield: 92%; (iii) 0.05 equiv $OsO_4$/*t*-BuOH, 3 equiv NMO/$H_2O$, acetone, rt, 24 h, yield: 83%; (iv) 18% HCl, $Et_2O$, rt, 24 h, yield: 52%; (v) 15% KOH, $CHCl_3$; (vi) starting from (−)-**5**, **6**: dry acetone as solvent, **7**: 10.5 equiv cyclohexanone, dry EtOH, **8**: 10.5 equiv diethyl ketone, dry EtOH, 3 equiv $NaBH_4$, yield: **6**: 59%, **7**: 85%, **8**: 18%; (vii) starting from (−)-**4**, 1.05 equiv PhCHO, $Et_3N$, then 2 equiv $NaBH_4$, dry EtOH, rt, yield: 81%; (viii) 1.05 equiv BnBr, $Et_3N$, MeCN, reflux, 24 h, yield: 30%; (ix) 35% HCHO/$H_2O$, $Et_2O$, rt, 1 h, yield: 97%; (x) 3 equiv LAH, THF, reflux, 1.5 h, yield: 38%.

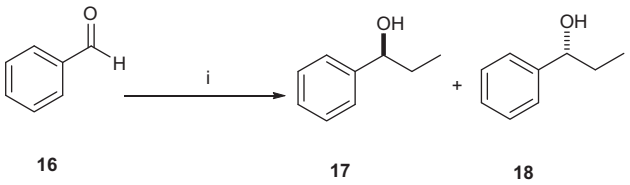
was introduced by the N-benzylation of (+)-**9** using benzyl bromide in MeCN in the presence of $Et_3N$. However, tertiary aminodiol (+)-**10** was isolated in only a moderate yield.

We recently found[21,22,31] that the ring closure of pinane- or carane-based aminodiols proceeded with high regioselectivity to give spiro-fused oxazolidines in the case of pinane derivatives, while the ring closure of carane-based aminodiols afforded fused 1,3-oxazines. The ring-closed products possessed higher catalytic activities than those of the aminodiol analogues. Since aminodiols **5**, **6**, and **9**–**15** are regioisomers of those reported earlier,[21,22,31] ring closure can lead to the formation of pinane-fused oxazolidines or 1,3-oxazines. When (+)-**9** was stirred with formaldehyde for 1 h, a regioselective ring closure was observed. The NMR data on (+)-**11** indicated that the hydroxy group on the tertiary carbon atom in (+)-**9** had been incorporated into a condensed oxazolidine ring. In order to increase the diversity in the substitution of the amine group, *N*-methyl-*N*-benzyl aminodiol (+)-**12** and *N*-methyl aminodiol (+)-**14** were prepared. The transformation of (+)-**11** into *N*-methyl-*N*-benzyl aminodiol (+)-**12** was accomplished by reduction with $LiAlH_4$ at reflux. Debenzylation of (+)-**12** in the presence of palladium-on-carbon catalyst gave *N*-methyl aminodiol (+)-**14**. Under similar reaction conditions as those used for the preparation of (+)-**11**, the ring closure of (+)-**14** displayed the same regioselectivity, furnishing oxazolidine (−)-**15** in good yields (Scheme 2).

### 2.2. Application of aminodiols as chiral ligands in the enantioselective addition of diethylzinc to benzaldehyde

Aminodiols and their ring-closed derivatives **5**–**15** were applied as chiral ligands in the addition of diethylzinc to benzaldehyde, resulting in 1-phenyl-1-propanol enantiomers **17** and **18** (Fig. 1, Scheme 3).

Catalysts **5**–**15** were applied in a 10% molar ratio and the reactions were performed at room temperature in *n*-hexane. The results are presented in Table 1. The enantiomeric purity of the 1-phenyl-1-propanol obtained was determined by GC on a CHIRASIL-DEX CB column, according to the literature.[15,42,43] In all cases, the (*R*)-enantiomer of **18** predominated, while the enantioselectivity of the reaction varied from low to moderate ee (Table 1). The results with catalysts (−)-**5**, (+)-**8**, (+)-**10** and (+)-**14** were unsatisfactory, but with (+)-**6**, (+)-**7** and (+)-**12**, moderate increases in enantioselectivity were observed. The best ee value (61%) was obtained when the *N*-benzyl derivative (+)-**9** was applied. It is interesting to note that in our previous studies on regioisomeric aminodiols,[21] the addition of diethylzinc to aldehydes exhibited the opposite selectivity, resulting in (*S*)-1-phenyl-1-propanol as the major product, with the catalytic activity increasing in the sequence $NH_2 < NHR^1 < NR^1R^2$. Since the ring-closed aminodiol derivatives in our former experiments displayed a higher catalytic activity in the aforementioned model reaction, pinane-fused oxazolidines (+)-**11** and (−)-**15** were also applied. However, only lower




**Scheme 3.** Reagents and conditions: (i) $Et_2Zn$/*n*-hexane, 10 mol % catalyst **5**–**15**, rt, Ar atm, yield: 73–86%.

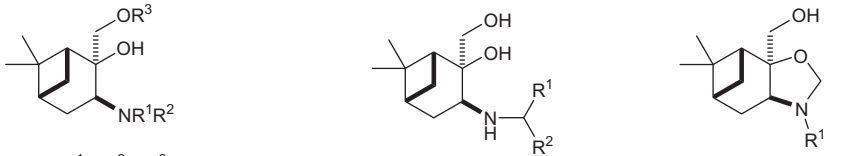
enantioselectivities were observed. The results were similar when the secondary alcohol functional group underwent O-alkylation, resulting in (+)-**13** (Scheme 2). Our results suggest that tridentate pinane-based aminodiols with a secondary amino function are more efficient catalysts than those containing a primary or tertiary amino group.

In order to rationalize the experimental findings, quantum chemical molecular modelling calculations were performed on the Noyori μ-oxo-complex formed by (+)-**9**. The calculation protocol utilized herein was described earlier,[29] but this time, full RHF/LANL2DZ optimization was carried out in the final stage (Table 2). Two main reaction pathways were proposed based on the coordinating hydroxyl groups in the μ-oxo-complex tertiary-OH and the primary-OH. The ethyl groups were replaced by methyl groups in order to eliminate conformational freedom because this modification was not expected to cause significant errors in the trends of relative energies. The μ-oxo transition state possesses four stereogenic centres, leading to 16 diastereomers, which were optimized by using the transition state-searching algorithm implemented in Gaussian03. The diastereomers are designated by their absolute chirality on Zn1 in the heterocyclic ring, on the secondary nitrogen, and by the *syn*- or *anti*-position of the transferring Zn2-attached alkyl group relative to the alkyl group on Zn1 (Fig. 2). Finally the complexes were also distinguished on the basis of the configuration of the carbon at the reaction centre.

The transition state search did not converge for the (*R*,*S*)_*syn* class of complexes for steric reasons; only high energy structures were obtained. Nevertheless, Table 2 reveals that the three lowest-energy transition states produce an (*R*)-configuration within the energy window of 2 kcal/mol. This modelling result is in good correlation with the experimentally observed selectivity for **9**.

## 3. Conclusions

In conclusion, we have developed a library of new chiral pinane-based aminodiols **5**–**15**, which may serve as chiral building blocks in the asymmetric synthesis of potential pharmacons, or be used as chiral ligands in enantioselective syntheses. The substituents influence the enantioselectivity in the reaction of diethylzinc with benzaldehyde in the sequence $NH_2 < NRR < NHR$. The ring




(-)-**5**: $R^1 = R^2 = R^3 = H$
(+)-**9**: $R^1 = R^3 = H$, $R^2 = PhCH_2$
(+)-**10**: $R^1 = R^2 = PhCH_2$, $R^3 = H$
(+)-**12**: $R^1 = Me$, $R^2 = PhCH_2$, $R^3 = H$
(+)-**13**: $R^1 = Me$, $R^2 = R^3 = PhCH_2$
(+)-**14**: $R^1 = R^3 = H$, $R^2 = Me$

(+)-**6**: $R^1 = R^2 = Me$
(+)-**7**: $R^1 = R^2 = (CH_2)_5$
(+)-**8**: $R^1 = R^2 = Et$

(+)-**11**: $R^1 = PhCH_2$
(-)-**15**: $R^1 = Me$

**Figure 1.** Chiral ligands for the enantioselective synthesis of 1-phenyl-1-propanol.

**Table 1**
Asymmetric addition of diethylzinc to benzaldehyde catalysed by ligands **5**–**15**

| Entry | Catalyst (10 mol %) | Yield[a] (%) | ee[b] (%) | Configuration of major product[c] |
|---|---|---|---|---|
| 1 | (−)-**5** | 83 | 1 | (*R*) |
| 2 | (+)-**6** | 79 | 40 | (*R*) |
| 3 | (+)-**7** | 76 | 19 | (*R*) |
| 4 | (+)-**8** | 81 | 3 | (*R*) |
| 5 | (+)-**9** | 85 | 61 | (*R*) |
| 6 | (+)-**10** | 80 | 1 | (*R*) |
| 7 | (+)-**11** | 75 | 27 | (*R*) |
| 8 | (+)-**12** | 73 | 26 | (*R*) |
| 9 | (+)-**13** | 86 | 6 | (*R*) |
| 10 | (+)-**14** | 82 | 1 | (*R*) |
| 11 | (−)-**15** | 77 | 8 | (*R*) |

[a] Isolated yields.
[b] Determined from the crude product by chiral GC (CHIRASIL-DEX CB column).
[c] Determined by comparing the $t_R$ of the GC analysis and the specific rotation with the literature data.[33,34]

**Table 2**
Ab initio RHF/LanL2DZ energies calculated for μ-oxo complexes **9**

| | E(RHF) (a.u.) | (E-Emin) (kcal/mol) | Product configuration |
|---|---|---|---|
| (*S*,*R*)_*syn*_$CH_2OH$ | −1450.829635 | 0.00 | (*R*) |
| (*S*,*S*)_*anti*_OH | −1450.826875 | 1.73 | (*R*) |
| (*S*,*R*)_*anti*_OH | −1450.826494 | 1.97 | (*R*) |
| (*S*,*R*)_*syn*_$CH_2OH$ | −1450.825875 | 2.36 | (*S*) |
| (*R*,*R*)_*anti*_$CH_2OH$ | −1450.82567 | 2.49 | (*R*) |
| (*S*,*S*)_*syn*_$CH_2OH$ | −1450.825244 | 2.76 | (*R*) |
| (*S*,*S*)_*anti*_OH | −1450.823476 | 3.86 | (*S*) |
| (*S*,*R*)_*anti*_OH | −1450.823133 | 4.08 | (*S*) |
| (*R*,*R*)_*syn*_$CH_2OH$ | −1450.822738 | 4.33 | (*S*) |
| (*S*,*S*)_*syn*_$CH_2OH$ | −1450.820994 | 5.42 | (*S*) |
| (*R*,*R*)_*anti*_$CH_2OH$ | −1450.820820 | 5.53 | (*S*) |
| (*S*,*R*)_*anti*_$CH_2OH$ | −1450.819587 | 6.30 | (*R*) |
| (*S*,*R*)_*syn*_OH | −1450.819388 | 6.43 | (*R*) |
| (*S*,*S*)_*anti*_$CH_2OH$ | −1450.817439 | 7.65 | (*R*) |
| (*R*,*S*)_*anti*_CH2OH | −1450.817112 | 7.86 | (*R*) |
| (*R*,*R*)_*anti*_OH | −1450.816756 | 8.08 | (*R*) |
| (*R*,*R*)_*anti*_OH | −1450.815029 | 9.17 | (*S*) |
| (*R*,*R*)_*syn*_OH | −1450.814432 | 9.54 | (*R*) |
| (*R*,*S*)_*anti*_$CH_2OH$ | −1450.812966 | 10.46 | (*S*) |
| (*R*,*R*)_*syn*_$CH_2OH$ | −1450.812954 | 10.47 | (*R*) |
| (*R*,*R*)_*syn*_OH | −1450.811653 | 11.28 | (*S*) |
| (*S*,*R*)_*syn*_OH | −1450.810544 | 11.98 | (*S*) |
| (*S*,*S*)_*syn*_OH | −1450.810184 | 12.21 | (*S*) |
| (*R*,*S*)_*anti*_OH | −1450.807678 | 13.78 | (*R*) |
| (*R*,*S*)_*anti*_OH | −1450.798307 | 19.66 | (*S*) |
| (*S*,*S*)_*syn*_OH | −1450.77621 | 33.52 | (*R*) |
| (*S*,*R*)_*anti*_$CH_2OH$ | −1450.772119 | 36.09 | (*S*) |

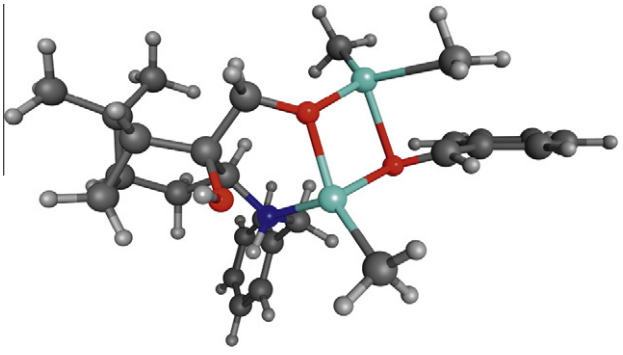


**Figure 2.** The lowest-energy transition state [(*S*,*R*)_*syn*_$CH_2OH$, (*R*)] obtained for the μ-oxo complex of **9**.

closure of the aminodiols proceeds with excellent regioselectivity, resulting exclusively in pinane-fused oxazolidines. Amongst these pinane-based aminodiols, derivatives bearing a secondary amino group proved to be good catalysts in the enantioselective synthesis of (*R*)-1-phenyl-1-propanol, with a selectivity opposite to that reported recently for their regioisomeric analogues.[21]

## 4. Experimental

### 4.1. General

$^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer (400 MHz, $\delta = 0$ (TMS)), in an appropriate solvent. Chemical shifts are expressed in ppm ($\delta$) relative to TMS as internal reference. *J* values are given in Hz. FT-IR spectra were recorded on a Perkin-Elmer Spectrum 100 instrument. Microanalyses were performed on a Perkin-Elmer 2400 elemental analyser. GC measurements were made on a Perkin-Elmer Autosystem XL GC, consisting of a Flame Ionization Detector and a Turbochrom Workstation data system (Perkin–Elmer Corporation Norwalk, USA). The column used for the direct separation of enantiomers was a CHIRASIL-DEX CB column (2500 × 0.25 mm I.D.). Optical rotations were obtained with a Perkin-Elmer 341 polarimeter. Melting points were determined on a Kofler apparatus and are uncorrected. Chro-

matographic separations were carried out on Merck Kieselgel 60 (230–400 mesh ASTM). Reactions were monitored with Merck Kieselgel 60 F254-precoated TLC plates (0.25 mm thickness). All the chemicals and solvents were used as supplied. For the ab initio calculations, the molecular structure, stereochemistry and geometry of the μ-oxo complex were defined exclusively in terms of their z-matrix internal coordinate system. The transition state optimizations were carried out in two stages. We used the transition state search algorithm as implemented in the Gaussian 03 program suite. The initial structures were preoptimized at the PM3 level of theory, then the production run was performed using the RHF method, with the LanL2DZ basis set. The converged structures contained a single negative value in their Hessian. Compound (+)-**2** was prepared from commercially available (1*R*)-(−)-myrtenol (Sigma–Aldrich) according to the literature;[32] all its spectroscopic data and physical properties were similar to those reported therein.

### 4.2. Preparation of 2,2,2-trichloro-*N*-((1*R*,2*R*,3*S*,5*R*)-2-hydroxy-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-3-yl)acetamide (+)-3

*Method A*: 2,2,2-trichloro-*N*-((1*R*,3*S*,5*R*)-6,6-dimethyl-2-methylenebicyclo[3.1.1]heptan-3-yl)acetamide (+)-**2** (1.00 g, 3.37 mmol) in EtOH (17 mL) was added dropwise to $KMnO_4$ (1.04 g, 6.75 mmol) and $MgSO_4$ (0.81 g, 6.75 mmol) in $H_2O$ (3 mL) at 0 °C. After stirring for 2 h, the mixture was filtered through a Celite pad and washed with EtOAc. The EtOH was evaporated off from the mixture under reduced pressure and the residue obtained was dissolved in $H_2O$ and extracted with EtOAc (3 × 20 mL). The combined organic phase was dried ($Na_2SO_4$) and evaporated. The crude product was purified by column chromatography (*n*-hexane/EtOAc = 2:1).

*Method B*: to 2,2,2-trichloro-*N*-((1*R*,3*S*,5*R*)-6,6-dimethyl-2-methylenebicyclo[3.1.1]heptan-3-yl)acetamide (+)-**2** (0.60 g, 2.0 mmol) in acetone (10 mL) were added 4-methylmorpholine-4-oxide (1.24 mL, 50% aqueous solution) and $OsO_4$ (1.28 mL, 2.0% *t*-BuOH solution). The reaction mixture was stirred for 24 h at room temperature. The reaction was then quenched by the addition of saturated aqueous $Na_2SO_4$ (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phase was dried ($Na_2SO_4$) and evaporated. The crude product was purified by column chromatography (*n*-hexane/EtOAc = 2:1). Compound (+)-**3**: *Method A*: 0.11 g (10%); *Method B*: 0.55 g (83%), yellow crystalline powder, mp 85–88 °C, $[\alpha]_D^{20} = +18.0$ (*c* 0.125, MeOH); $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 0.96 (3H, s), 1.17 (1H, t, *J* = 7.2 Hz), 1.24 (3H, s, $CH_3$), 1.44 (1H, d, *J* = 9.7 Hz), 1.53 (1H, dd, *J* = 6.6, 13.7 Hz), 1.87–1.90 (1H, m), 1.98 (1H, s), 2.10–2.18 (2H, m), 3.93–3.98 (1H, m), 4.03 (1H, q, *J* = 7.5 Hz), 4.70 (1H, *t*, *J* = 5.6 Hz), 5.02 (1H, s), 8.30 (1H, d, *J* = 6.56 Hz). $^{13}$C NMR (DMSO-$d_6$) $\delta$ (ppm): 23.66, 27.46, 27.69, 35.24, 38.07, 39.96, 46.38, 48.40, 59.69, 67.51, 75.01, 159.97. IR (KBr, $cm^{-1}$) $\nu$ = 3465, 3370, 2917, 1678, 1491, 825. Anal. Calcd for $C_{12}H_{18}Cl_3NO_3$ (329.04): C, 43.59; H, 5.49; N, 4.24. Found: C, 43.32; H, 5.21; N, 4.27.

### 4.3. Preparation of (1*R*,2*R*,3*S*,5*R*)-3-amino-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-ol hydrochloride (−)-4

A solution of (+)-**3** (4.22 g, 12.7 mmol) in $Et_2O$ (26 mL) was stirred with 106 mL of 18% aqueous HCl at room temperature. After 24 h, the mixture was evaporated to dryness, and the residue was recrystallized from EtOH–$Et_2O$. Compound (−)-**4**: 1.46 g (52%); colourless crystalline powder, mp 239–245 °C; $[\alpha]_D^{20} = -4.0$ (*c* 0.125, MeOH); $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 0.87 (3H, s), 1.20 (3H, s), 1.57 (1H, d, *J* = 10.4 Hz), 1.65–1.71 (1H, m), 1.83–1.90 (1H, m), 1.97 (1H, *t*, *J* = 5.3 Hz), 2.09–2.14 (1H, m), 2.23–2.29 (1H, m), 3.27–3.33 (1H, m), 3.46–3.51 (2H, m),4.05 (2H, s) 4.99–5.02 (1H, m), 7.70 (2H, s) $^{13}$C NMR (DMSO-$d_6$) $\delta$ (ppm): 23.59, 26.81, 27.44, 32.21, 38.05, 39.76, 45.85, 48.60, 68.24, 74.21. IR (KBr, $cm^{-1}$) $\nu$ = 3231, 2940, 1599, 1522, 841. Anal. Calcd for $C_{10}H_{20}ClNO_2$ (221,12): C, 54.17; H, 9.09; N, 6.32. Found: C, 54.45; H, 9.24; N, 6.03.

#### 4.3.1. Preparation of (1*R*,2*R*,3*S*,5*R*)-3-amino-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-ol (−)-5

To compound (−)-**4** (1.46 g, 6.6 mmol) were added 5 mL of 15% aqueous KOH solution and the mixture was extracted with $CHCl_3$ (3 × 30 mL). The organic layer was dried ($Na_2SO_4$) and evaporated, resulting in (−)-**5**. Compound (−)-**5**: 0.99 g (81%); colourless crystalline powder, mp 124–128 °C; $[\alpha]_D^{20} = -11.0$ (*c* 0.125, MeOH); $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 0.91 (3H, s), 1.19 (3H, s), 1.25 (1H, dd, *J* = 2.8, 6.9 Hz), 1.28 (1H, d, *J* = 9.6 Hz), 1.76–1.80 (1H, m), 1.89 (1H, *t*, *J* = 5.7 Hz), 1.99–2.05 (1H, m), 2.24–2.31 (1H, m), 3.12 (1H, d, *J* = 10.9 Hz), 3.18 (1H, dd, *J* = 6.7, 9.6 Hz), 3.27 (1H, d, *J* = 10.9 Hz). $^{13}$C NMR (DMSO-$d_6$) $\delta$ (ppm): 23.82, 27.64, 28.02, 37.50, 37.97, 40.37, 45.87, 48.80, 69.69, 73.95. IR (KBr, $cm^{-1}$) $\nu$ = 3359, 2910, 1603, 1485, 1059, 938. Anal. Calcd for $C_{10}H_{19}NO_2$ (185.26): C, 64.83; H, 10.34; N, 7.56. Found: C, 64.62; H, 10.14; N, 7.66.

### 4.4. Preparation of (1*R*,2*R*,3*S*,5*R*)-3-isopropylamino-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-ol (+)-6

A solution of (−)-**5** (0.25 g, 1.35 mmol) in dry acetone (15 mL) was stirred for 2 h at room temperature and then evaporated to dryness. After evaporation of the solvent, the residue was dissolved in dry EtOH (15 mL), and $NaBH_4$ (0.15 g, 4.05 mmol) was added cautiously. The reaction mixture was stirred for 24 h at room temperature. The solvent was then removed and the residue was dissolved in $H_2O$ and extracted with $CHCl_3$ (3 × 20 mL). The organic layer was dried ($Na_2SO_4$) and evaporated. The crude product was purified by column chromatography ($CHCl_3$/MeOH = 2:1). Compound (+)-**6**: 0.18 g (59%); orange crystals, mp 36–38 °C; $[\alpha]_D^{20} = +14.0$ (*c* 0.125, MeOH); $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 0.94 (3H, s), 1.08 (3H, d, *J* = 6.3 Hz), 1.12 (3H, d, *J* = 6.3 Hz), 1.23–1.25 (4H, m), 1.35–1.41 (1H, m), 1.86–1.91 (1H, m), 2.14–2.22 (2H, m), 2.55–2.63 (2H, m), 2.86–2.95 (2H, m), 3.42 (2H, q, *J* = 10.7, 14.9 Hz), 3.72 (2H, s). $^{13}$C NMR ($CDCl_3$) $\delta$ (ppm): 23.51, 23.76, 24.09, 27.56, 27.79, 39.23, 40.76, 48.46, 48.60, 51.52, 63.85, 70.52, 74.34. IR (KBr, $cm^{-1}$) $\nu$ = 3359, 2920, 1408, 1069, 891. Anal. Calcd for $C_{13}H_{25}NO_2$ (227.34): C, 68.68; H, 11.08; N, 6.16. Found: C, 68.45; H, 11.28; N, 6.01.

### 4.5. General procedure for the synthesis of (+)-7 and (+)-8

To a solution of (−)-**5** (0.10 g, 0.54 mmol) in dry EtOH (25 mL) was added the appropriate ketone (5.67 mmol) and the mixture was stirred at room temperature. After 2 h, the solvent was removed under reduced pressure. The residue was dissolved in dry EtOH (25 mL), after which $NaBH_4$ (0.04 g, 1.08 mmol) was added, and the solution was stirred for 24 h at room temperature. The solvent was evaporated off and the residue was dissolved in $H_2O$ and extracted with $CHCl_3$ (3 × 30 mL). The organic layer was dried ($Na_2SO_4$) and evaporated. The crude product was purified by column chromatography [(+)-**7**: toluene/EtOH = 1:1, (+)-**8**: $CHCl_3$/MeOH = 2:1].

#### 4.5.1. (1*R*,2*R*,3*S*,5*R*)-3-Cyclohexylamino-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-ol (+)-7

Compound (+)-**7**: 0.12 g (85%); yellow crystals, mp 81–89 °C; $[\alpha]_D^{20} = +9.0$ (*c* 0.125, MeOH); $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 0.93 (3H, s), 0.98–1.07 (1H, m), 1.24–1.28 (9H, m), 1.34–1.39 (1H, m), 1.50–1.62 (2H, m), 1.69–1.74 (2H, m), 1.85–1.98 (2H, m), 2.16

(1H, d, $J$ = 5.8 Hz), 2.44–2.51 (1H, m), 2.55–2.61 (1H, m), 2.95 (1H, dd, $J$ = 5.4, 10.0 Hz), 3.39 (1H, s), 3.56–3.62 (1H, m). $^{13}$C NMR ($CDCl_3$) $\delta$ (ppm): 24.10, 25.26, 25.63, 26.07, 27.59, 27.79, 34.34, 35.70, 38.61, 39.63, 40.78, 48.38, 51.11, 56.31, 70.49, 74.23. IR (KBr, cm$^{-1}$) $\nu$ = 3366, 2927, 1453, 1067, 893. Anal. Calcd for $C_{16}H_{29}NO_2$ (267.22): C, 71.86; H, 10.93; N, 5.24. Found: C, 71.68; H, 10.77; N, 5.46.

#### 4.5.2. (1*R*,2*R*,3*S*,5*R*)-3-Pentan-3-ylamino-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-ol (+)-8

Compound (+)-**8**: 0.02 g (18%); yellow oil; $[\alpha]_D^{20} = +5.0$ ($c$ 0.125, MeOH); $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 0.87–0.95 (9H, m), 1.25–1.31 (5H, m), 1.35–1.60 (4H, m), 1.87–1.92 (1H, m), 2.14–2.21 (2H, m), 2.51–2.61 (2H, m), 2.97 (1H, dd, $J$ = 5.4, 10.1 Hz), 3.42 (2H, s). $^{13}$C NMR ($CDCl_3$) $\delta$ (ppm): 9.49, 10.31, 24.17, 26.12, 26.34, 27.61, 27.79, 29.86, 38.80, 40.82, 48.61, 51.89, 60.01, 70.55, 74.64. IR (KBr, cm$^{-1}$) $\nu$ = 3420, 2924, 1630, 1462, 1065. Anal. Calcd for $C_{15}H_{29}NO_2$ (255.22): C, 70.54; H, 11.45; N, 5.48. Found: C, 70.37; H, 11.27; N, 5.57.

### 4.6. Preparation of (1*R*,2*R*,3*S*,5*R*)-3-benzylamino-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-ol (+)-9

To a mixture of (−)-**4** (0.20 g, 0.9 mmol) and $Et_3N$ (0.18 g, 1.8 mmol) in dry EtOH (15 mL), benzaldehyde (0.10 g, 0.95 mmol) was added, and the mixture was stirred for 2 h at room temperature. After evaporation of the solvent, the residue was dissolved in dry EtOH (15 mL), after which $NaBH_4$ (0.068 g, 1.8 mmol) was added portionwise. The reaction mixture was stirred for 24 h at room temperature, the solvent was then removed and the residue was dissolved in $H_2O$ and extracted with $CHCl_3$ (3 × 20 mL). The combined organic layer was dried ($Na_2SO_4$) and evaporated. The crude product was purified by column chromatography ($CHCl_3$/MeOH = 9:1). Compound (+)-**9**: 0.20 g (81%); colourless crystalline powder, mp 74–78 °C, $[\alpha]_D^{20} = +10.0$ ($c$ 0.125, MeOH); $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 0.90 (3H, s), 1.25 (3H, s), 1.32 (1H, d, $J$ = 10.3 Hz), 1.46 (1H, ddd, $J$ = 2.6, 5.7, 13.7 Hz), 1.88–1.92 (1H, m), 2.15 (1H, $t$, $J$ = 5.9 Hz), 2.18–2.24 (1H, m), 2.48–2.55 (1H, m), 3.02 (1H, dd, $J$ = 5.7, 9.9 Hz), 3.43 (2H, dd, $J$ = 10.8, 24.2 Hz), 3.90 (2H, s), 7.27–7.37 (5H, m). $^{13}$C NMR ($CDCl_3$) $\delta$ (ppm): 24.07, 27.63, 27.78, 37.68, 38.53, 40.77, 48.84, 52.97, 53.62, 70.70, 74.77, 127.68, 128.42, 128.81. IR (KBr, cm$^{-1}$) $\nu$ = 3345, 2904, 1935, 1862, 1798, 1740. Anal. Calcd for $C_{17}H_{25}NO_2$ (275.39): C, 74.14; H, 9.15; N, 5.09. Found: C, 73.97; H, 8.99; N, 5.19.

### 4.7. Preparation of (1*R*,2*R*,3*S*,5*R*)-3-dibenzylamino-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-ol (+)-10

To a solution of (+)-**9** (0.10 g, 0.36 mmol) and $Et_3N$ (0.11 g, 1.1 mmol) in dry MeCN (5 mL), benzyl bromide (0.065 g, 0.42 mmol) was added. When the reaction was complete (monitored by means of TLC), the mixture was evaporated to dryness, and the residue was dissolved in $H_2O$ (3 mL) and extracted with $CHCl_3$ (3 × 5 mL). The combined organic layer was dried ($Na_2SO_4$) and evaporated. The crude product was purified by column chromatography ($n$-hexane/EtOAc = 2:1). Compound (+)-**10**: 0.04 g (30%); colourless crystalline powder, mp 128–130 °C; $[\alpha]_D^{20} = +11.0$ ($c$ 0.125, MeOH); $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 0.80 (3H, s), 1.24–1.28 (4H, m, $CH_3$, 1H), 1.47 (1H, d, $J$ = 11.1 Hz), 1.57 (1H, s), 1.99–2.29 (5H, m), 2.98 (2H, s), 3.25 (1H, s), 3.48 (2H, d, $J$ = 13.0 Hz), 4.06 (2H, s), 7.26–7.35 (10H, m). $^{13}$C NMR ($CDCl_3$) $\delta$ (ppm): 23.77, 24.91, 27.49, 27.93, 32.53, 38.40, 40.86, 47.48, 54.35, 56.75, 70.10, 77.67, 127.65, 128.84, 129.06. IR (KBr, cm$^{-1}$) $\nu$ = 3431, 2921, 1630, 1452, 747. Anal. Calcd for $C_{24}H_{31}NO_2$ (365.51): C, 78.86; H, 8.55; N, 3.83. Found: C, 78.50; H, 8.20; N, 4.02.

### 4.8. General procedure for the synthesis of oxazolidines (+)-11 and (−)-15

At first, 5 mL of 35% aqueous formaldehyde was added to a solution of (+)-**9** or (+)-**14** (0.43 mmol) in 2 mL of $Et_2O$. The mixture was stirred at room temperature for 1 h, then made alkaline with 10% aqueous KOH and extracted with $Et_2O$ (3 × 15 mL). The combined organic phase was dried ($Na_2SO_4$) and evaporated. The crude product was purified by column chromatography [(+)-**11**: $n$-hexane/EtOAc = 4:1, (−)-**15**: $n$-hexane/EtOAc = 3:2].

#### 4.8.1. [(1*R*,2*R*,6*S*,8*R*)-5-Benzyl-9,9-dimethyl-3-oxa-5-azatricyclo[6.1.1.0$^{2,6}$]dec-2-yl]methanol (+)-11

Compound (+)-**11**: 0.12 g (97%); oil; $[\alpha]_D^{20} = +3.0$ ($c$ 0.125, MeOH); $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 0.81 (3H, s), 1.21 (3H, s), 1.73–1.86 (3H, m), 1.91–2.09 (3H, m), 2.68 (1H, d, $J$ = 7.9 Hz), 3.28–3.40 (2H, m), 3.53 (1H, dd, $J$ = 5.3, 11.8 Hz), 3.91 (1H, d, $J$ = 13.2 Hz), 3.98 (1H, s), 4.31 (1H, s), 4.63 (1H, $t$, $J$ = 7.4 Hz), 7.21–7.34 (5H, m). $^{13}$C NMR (DMSO-$d_6$) $\delta$ (ppm): 23.14, 24.12, 27.03, 32.32, 37.24, 40.25, 45.19, 54.76, 57.16, 65.33, 84.39, 88.24, 126.88, 128.18, 128.28. IR (KBr, cm$^{-1}$) $\nu$ = 3441, 2925, 1955, 1808, 1604, 1453, 1071, 698. Anal. Calcd for $C_{18}H_{25}NO_2$ (287.19): C, 75.22; H, 8.77; N, 4.87. Found: C, 75.07; H, 8.65; N, 4.99.

#### 4.8.2. [(1*R*,2*R*,6*S*,8*R*)-5,9,9-Trimethyl-3-oxa-5-azatricyclo[6.1.1.0$^{2,6}$]dec-2-yl]methanol (−)-15

Compound (+)-**15**: 0.03 g (41%); colourless crystalline powder, mp 44–46 °C; $[\alpha]_D^{20} = -11.0$ ($c$ 0.125, MeOH); $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 0.86 (3H, s), 1.29 (3H, s), 1.17–1.85 (3H, m), 1.92–1.98 (1H, m), 2.00–2.08 (1H, m), 2.12–2.20 (1H, m), 2.28 (1H, $t$, $J$ = 5.5 Hz), 2.33 (3H, s), 2.37–2.43 (1H, m), 3.56 (1H, d, $J$ = 11.5 Hz), 3.65 (1H, d, $J$ = 11.5 Hz), 3.99 (1H, s), 4.60 (1H, s). $^{13}$C NMR ($CDCl_3$) $\delta$ (ppm): 23.77, 24.68, 27.32, 31.40, 36.60, 37.96, 40.98, 45.28, 60.38, 66.34, 86.27, 89.37. IR (KBr, cm$^{-1}$) $\nu$ = 3425, 2926, 1458, 1067. Anal. Calcd for $C_{12}H_{21}NO_2$ (211.16): C, 68.21; H, 10.02; N, 6.63. Found: C, 68.49; H, 10.15; N, 6.57.

### 4.9. Preparation of (1*R*,2*R*,3*S*,5*R*)-3-benzyl(methyl)amino-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-ol (+)-12

To a stirred suspension of $LiAlH_4$ (0.48 g, 12.63 mmol) in dry THF (90 mL), a solution of (+)-**11** (1.45 g, 5.05 mmol) in THF (15 mL) was added at 0 °C. The reaction mixture was refluxed for 1.5 h, and a mixture of $H_2O$ (0.5 mL) and THF (25 mL) was then added dropwise with cooling. The inorganic material was filtered off and washed with THF. The filtrate was dried ($Na_2SO_4$) and evaporated. The crude product was purified by column chromatography (toluene/EtOH = 4:1). Compound (+)-**12**: 0.56 g (38%); oil; $[\alpha]_D^{20} = +8.0$ ($c$ 0.125, MeOH); $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 0.91 (3H, s), 1.26 (3H, s), 1.39 (1H, d, $J$ = 10.6 Hz), 1.96–2.11 (3H, m), 2.15 (1H, $t$, $J$ = 5.5 Hz), 2.21–2.27 (1H, m), 2.43 (3H, s), 3.20 (1H, s), 3.32 (2H, s), 3.66 (1H, d, $J$ = 13.1 Hz), 3.88 (1H, d, $J$ = 13.1 Hz), 7.27–7.37 (5H, m). $^{13}$C NMR ($CDCl_3$) $\delta$ (ppm): 23.98, 24.59, 27.19, 27.84, 38.50, 39.65, 40.74, 46.87, 58.40, 61.57, 70.22, 77.42, 127.78, 128.75, 129.23. IR (KBr, cm$^{-1}$) $\nu$ = 3433, 2913, 1946, 1602, 1457, 700. Anal. Calcd for $C_{18}H_{27}NO_2$ (289.41): C, 74.70; H, 9.40; N, 4.84. Found: C, 74.35; H, 9.06; N, 5.16.

### 4.10. Preparation of (1*R*,2*R*,3*S*,5*R*)-3-(*N*-Benzyl-*N*-methylamino)-2-benzyloxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-ol (+)-13

A solution of (+)-**12** (0.20 g, 0.69 mmol) in THF (5 mL) was added to a suspension of NaH (60% in mineral oil; 0.034 g, 0.87 mmol) in THF (3 mL) at 0 °C under an Ar atmosphere. The

mixture was stirred for 30 min, and a solution of benzyl bromide (0.75 mmol, 0.13 g) in THF (3 mL) was then added by syringe. The mixture was stirred for 8 h at reflux temperature, after which $H_2O$ (1 mL) was added dropwise. The THF was evaporated off, after which $H_2O$ was added (5 mL) and the mixture was extracted with EtOAc (3 × 15 mL). The organic layer was dried ($Na_2SO_4$) and evaporated. The resulting oil was purified by column chromatography (*n*-hexane/EtOAc = 4:1). Compound (+)-**13**: 0.11 g (44%); oil; $[\alpha]_D^{20} = +30.0$ (*c* 0.125, MeOH); $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 0.73 (3H, s), 1.15–1.16 (4H, m), 1.37 (1H, d, *J* = 10.5 Hz), 1.84–1.90 (2H, m), 1.97–2.03 (1H, m), 2.05 (1H, *t*, *J* = 5.7 Hz), 2.09–2.15 (1H, m), 2.27 (3H, s), 3.11–3.17 (2H, m), 3.34 (1H, d, *J* = 11.6 Hz), 3.63 (1H, d, *J* = 13.5 Hz), 3.74 (1H, d, *J* = 13.5 Hz), 4.44 (1H, d, *J* = 12.3 Hz), 4.52 (1H, d, *J* = 12.3 Hz), 7.16–7.26 (10 H, m). $^{13}$C NMR ($CDCl_3$) $\delta$ (ppm): 24.04, 25.13, 26.91, 27.83, 38.38, 39.32, 40.78, 47.94, 58.45, 61.72, 73.65, 77.26, 78.33, 127.10, 127.59, 127.97, 128.40, 129.06. IR (KBr, $cm^{-1}$) $\nu$ = 3548, 2909, 1948, 1871, 1807, 1702, 1453, 698. Anal. Calcd for $C_{25}H_{33}NO_2$ (379.25): C, 79.11; H, 8.76; N, 3.69. Found: C, 79.37; H, 8.90; N, 3.54.

### 4.11. Preparation of (1*R*,2*R*,3*S*,5*R*)-2-hydroxymethyl-3-methylamino-6,6-dimethylbicyclo[3.1.1]heptan-2-ol (+)-14

To a suspension of palladium-on-carbon (5%, 0.10 g) in MeOH (10 mL), a solution of aminodiol (+)-**12** (0.35 g, 1.21 mmol) in MeOH (15 mL) was added. The mixture was stirred under an $H_2$ atmosphere at room temperature and atmospheric pressure. When the reaction was complete, as indicated by TLC, the solution was filtered through a Celite pad and the solvent was removed. The crude product was purified as the hydrochloride salt. The base liberated was a yellow oil. Compound (+)-**14**: 0.13 g (57%); oil, $[\alpha]_D^{20} = +9.0$ (*c* 0.125, MeOH), $^1$H NMR (DMSO-$d_6$) $\delta$ (ppm): 0.89 (3H, s), 1.18 (3H, s), 1.22 (2H, d, *J* = 9.8 Hz), 1.38–1.43 (1H, m), 1.77–1.81 (1H, m), 1.96 (1H, t, *J* = 5.8 Hz), 1.99–2.05 (1H, m), 2.30–2.34 (4H, m), 2.67 (1H, dd, *J* = 5.7, 9.6 Hz), 3.17 (1H, d, *J* = 11.2 Hz), 3.30 (1H, d, *J* = 11.2 Hz). $^{13}$C NMR (DMSO-$d_6$) $\delta$ (ppm): 23.78, 27.11, 27.70, 35.32, 35.94, 37.82, 40.14, 48.41, 55.10, 69.31, 74.25. IR (KBr, $cm^{-1}$) $\nu$ = 3453, 2909, 1558, 1321, 918. Anal. Calcd for $C_{11}H_{21}NO_2$ (199.16): C, 66.29; H, 10.62; N, 7.03. Found: C, 65.98; H, 10.51; N, 7.47.

### 4.12. General procedure for the reaction of aldehydes with diethylzinc in the presence of chiral catalyst (−)–5–(−)-15

To the respective catalyst (0.1 mmol) **5**–**15**, 1 M $Et_2Zn$ in *n*-hexane solution (3 mL, 3 mmol) was added under an argon atmosphere at room temperature. The reaction was stirred for 25 min at room temperature, and benzaldehyde (1 mmol) was then added to the solution, with subsequent stirring at room temperature for a further 20 h. The reaction was quenched with a saturated $NH_4Cl$ solution (15 mL) and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic phase was washed with $H_2O$ (10 mL), dried ($Na_2SO_4$) and evaporated under vacuum. The crude secondary alcohols obtained were purified by flash column chromatography (*n*-hexane/EtOAc = 4:1). The enantiomeric excess and absolute configuration of the resulting material were determined by chiral GC, using a chiral stationary phase (Chirasil-Dex CB column) at 90 °C for 1-phenyl-1-propanol **17** and **18** [$t_{R1}$ = 7.0 min for the (*S*)-isomer, $t_{R2}$ = 8.1 min for the (*R*)-isomer].[33,34] The direction of the specific rotation of each product was also checked.

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