Article

Synthesis and Investigation of Pinane-Based Chiral Tridentate Ligands in the Asymmetric Addition of Diethylzinc to Aldehydes

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Abstract: A library of pinane-based chiral aminodiols, derived from natural (−)-β-pinene, were prepared and applied as chiral catalysts in the addition of diethylzinc to aldehydes. (−)-β-Pinene was reacted to provide 3-methylenenopinone, followed by a reduction of the carbonyl function to give a key allylic alcohol intermediate. Stereoselective epoxidation of the latter and subsequent ring opening of the resulting oxirane with primary and secondary amines afforded aminodiols. The regioselectivity of the ring closure of the N-substituted secondary aminodiols with formaldehyde was examined and exclusive formation of oxazolidines was observed. Treatment of the allylic alcohol with benzyl bromide provided the corresponding O-benzyl derivative, which was transformed into O-benzyl aminodiols by aminolysis. Ring closure of the N-isopropyl aminodiol derivative with formaldehyde resulted in spirooxazolidine. The obtained potential catalysts were applied in the reaction of both aromatic and aliphatic aldehydes to diethylzinc providing moderate to good enantioselectivities (up to 87% ee). Through the use of molecular modeling at an ab initio level, this phenomenon was interpreted in terms of competing reaction pathways. Molecular modeling at the RHF/LANL2DZ level of theory was successfully applied for interpretation of the stereochemical outcome of the reactions leading to display excellent (R) enantioselectivity in the examined transformation.

Keywords: (−)-β-pinene; 3-methylenenopinone, aminodiols; diethylzinc, chiral catalyst

1. Introduction

Chiral synthons, applied successfully in asymmetric homogenous and heterogeneous catalysis, have achieved increasing importance in organic chemistry in recent years [1–3]. The enantioselective addition of dialkylzinc to aldehydes catalyzed by different types of chiral ligands has been investigated intensively [4–6], because the preparation of enantiomerically pure or enriched alcohols is of considerable interest for the synthesis of bioactive compounds [7–9] and natural products [10,11].

Aromatic and aliphatic aminodiols bearing a 1,2- or a 1,3-aminoalcohol moiety have proven to be highly efficient building blocks [12–15]. They have been applied as starting materials in the stereoselective synthesis of compounds of pharmacological interest, including 1,3-oxazines [16], 1,3-thiazines [17–19] and 2-iminothiazolines [20]. In addition to their synthetic importance, aminodiols can also be applied as chiral ligands and auxiliaries in enantioselective transformations [21–24] including intramolecular radical cyclizations [25], intramolecular [2+2] photocycloaddition [26] and Grignard addition [27,28]. Therefore, it is not surprising that the preparation of new chiral aminodiols has been a topic of increased interest. Although numerous enantiopure chelating ligands have been
prepared [29–34], there is still a need for new types obtainable by concise syntheses from inexpensive starting materials.

Naturally occurring chiral monoterpenes such as (+)- and (–)-α-pinene [21,35,36], (+)-carene [37,38], (+)-camphor [31,39], (–)-menthone [34], (–)-fenchone [29], (–)-sabinol [40], (–)-myrtenol [21,41], (–)-pulegone [42], neoisopulegol [43] and (S)-perillyl alcohol [44] have been widely used as key intermediates for the synthesis of chiral catalysts and auxiliaries for asymmetric synthesis.

Besides their chemical interests, many compounds containing 1-amino-2,3-diol functionalities display remarkable pharmacological activities. For example, Abbott-aminodiol bears the core of the drug Zankiren® exhibiting renin-inhibitory activity [45,46]. Aminodiols have also been reported to have expressed biological properties such as a gastro-protective effect [47] or HIV protease [48] inhibition and antiviral activity [49–51].

In the present paper we report the diastereoselective synthesis of new aminodiol derivatives as potential chiral ligands in the asymmetric addition of Et2Zn to aldehydes starting from commercially available natural (−)-β-pinene. These compounds, the regioisomers of pinane-based 3-amino-1,2-diols, were prepared from α-pinene [36]. In addition, we planned to develop a molecular model through which the interpretation of the catalytic pathway of the reaction and the catalytic activities of the chiral aminodiol derivatives should be possible.

2. Results

2.1. Synthesis of Allylic Alcohol 4a

Key intermediate 3-methylenenopinone 3 was prepared from commercially available (−)-β-pinene 1 by oxidation with the NaIO₄/RuCl₃ system to afford (−)-nopinone 2. The resulting (−)-nopinone was converted into (−)-3-methylenenopinone 3 by applying formaldehyde in alkaline condition according to literature methods [52,53] (Scheme 1).

![Scheme 1. Preparation of (−)-3-methylenenopinone.](image)

Reduction of 3 with NaBH₄ in various solvents gave a mixture of 4a and 4b (Scheme 2, Table 1). It is important to note that whereas allylic alcohol 4a was formed in a highly stereoselective manner, 4b exists as a 4:1 mixture of two cis-diastereomers (*diexo* and *diendo*, based on ¹H-NMR measurement and comparison with data in the literature) [54,55].

![Scheme 2. (i) NaBH₄ (2 equ.) and CeCl₃·7H₂O (1 equ.), 0 °C, 0.5 h, 87%](image)
Table 1. Stereoselective reduction of 3 according to Scheme 1.

| Entry | Reductant | Additive | Solvent | T (°C) | t (h) | Ratio 4a/4b | Yield (%) |
|-------|-----------|----------|---------|--------|-------|-------------|-----------|
| 1     | NaBH₄     | -        | MeOH    | −20    | 6     | 3:1         | 86        |
| 2     | NaBH₄     | -        | MeOH    | 0      | 1     | 1:1         | 86        |
| 3     | NaBH₄     | CeCl₃    | MeOH    | 0      | 0.5   | 100:0       | 87        |
| 4     | NaBH₄     | -        | Et₂O    | 0      | 3     | 3:1         | 76        |
| 5     | NaBH₄     | -        | EtOH    | 0      | 48    | 1:3         | 84        |

[a] Based on ¹H-NMR measurements of the crude product. [b] Isolated, combined yield of 4a and 4b.

When Et₂O was applied as solvent, 4a was formed as the main product (4a:4b = 3:1), whereas the ratio of the two products in EtOH changed to 4a:4b = 1:3. In contrast, when MeOH was used as a solvent, the two products formed in a 1:1 ratio. In addition, it is interesting to note that the ratio of 4a and 4b also depended on the temperature. At −20 °C in MeOH, compound 4a was obtained as the major product (Table 1), although 4a and 4b could not be separated by conventional technics. Applying the condition of Luche reaction, in the presence of CeCl₃ as additive, 4a was obtained as the single product. This procedure not only allowed highly regioselective reduction, but also enhanced reaction rate. The probable reason is the effect of cerium, a hard Lewis acid. Despite its weak acidity, it certainly contributes to both the regioselectivity and the high reaction rate though the coordination to the oxygen of the carbonyl function [56].

2.2. Synthesis of (−)-β-Pinene-Based Aminodiols

Epoxidation of 4a with t-BuOOH in the presence of VO(acac)₂ as catalyst furnished epoxide 5 as a single product in a stereoselective reaction [57,58]. Since purification of epoxide 5 could not be effectively performed without its decomposition, the crude product with a purity of approximately 92% (based on ¹H NMR measurement) was treated with various amines to perform the aminolysis of the oxirane ring. Our previous results clearly demonstrated that when aminodiols were applied as catalysts, their N-substituents definitely influenced the enantioselectivity of their catalyzed reaction [22,37,59,60]. Consequently, aminodiol library 6–13 was prepared by aminolysis of 5 with secondary and primary amines in the presence of lithium perchlorate as catalyst (Scheme 3).

![Scheme 3](image_url)

6: R¹ = H, R² = Bn, 7: R¹ = H, R² = CH(Me)Ph (R), 8: R¹ = H, R² = CH(Me)Ph (S), 9: R¹ = H, R² = CH(Me)₂, 10: R¹ = Bn, R² = Bn, 11: R¹ = Bn, R² = CH(Me)Ph (R), 12: R¹ = Bn, R² = CH(Me)Ph (S), 13: R¹, R² = -(CH₂)₂CH(Bn),(CH₂)₂.

Scheme 3. (i) VO(acac)₂, 70% t-BuOOH (2 equ.), dry toluene, 25 °C, 12 h, 76% and (ii) R¹R²NH (2 equ.), LiClO₄ (1 equ.), MeCN, 70–80 °C, 6 h, 32%–94%.

Primary aminodiol 14 was obtained in moderate yield by debenzylation of the corresponding N-benzyl aminodiol 6 under standard condition by hydrogenation over Pd/C (Scheme 4).

The ring closure reaction of 6 and 9 aminodiols with formaldehyde was also investigated to study the regioselectivity of the reaction [38,42,60]. When these aminodiols were reacted with formaldehyde under mild conditions, spirooxazolidine 15 and 16 were obtained in highly regioselective ring closure, with similar regioselectivity as observed in the case of pinane-based regioisomers [36]. This regioselectivity, however, is opposite to those of the carene-based analogues reported recently (Scheme 4) [37,38].
Scheme 4. (i) From 6 (R = Bn), 5% Pd/C, H2 (1 atm), MeOH, 25 °C, 24 h, 74% and (ii) 35% HCHO, Et2O, 25 °C, 1 h, 98% (15, R = Bn), 40% (16, R = CH(Me)2).

On the other hand, to assess the importance of the secondary hydroxyl group in the catalytic application of our aminodiols, allylic alcohol 4a was transformed into O-benzyl derivative 17. The separation of 16 and benzyl bromide was unsuccessful using classical chromatography methods. Therefore, 17 was transformed with mCPBA to epoxide 18 and the latter could be easily purified (in contrast to its epoxyalcohol analogue 5) on a gram scale by simple column chromatography in good yield [61–64]. The aminolysis of the formed oxirane ring of 18 with different amines afforded O-benzyl aminodiols 19–22 (Scheme 5) [22,59].

Scheme 5. (i) 60% NaH (1 equ.), dry THF, 25 °C, 1 h; then BnBr (1.5 equ.), KI (1 equ.), 60–70 °C, 12 h, 62%; (ii) mCPBA (2 equ.), Na2HPO4. 2H2O (3 equ.), 25 °C, 2 h, 46% and (iii) RNH2 (2 equ.), LiClO4 (1 equ.), MeCN, 70–80 °C, 6 h, 30%–36%.

The relative configurations of both compounds 6–13 and 19–22 were assigned by means of NOESY experiments: reliable NOE signals were observed between the H-10 and H-2, H-6 as well as H-2 and H-6 protons (Figure 1).

Figure 1. Determination of the structure of aminodiols by NOESY.

The regioselectivity of the ring closure of 22 with formaldehyde resulting in spirooxazolidine 23 (Scheme 6) was also investigated [38,42,60].
2.3. Application of Aminodiols as Chiral Ligands for Catalytic Addition of Diethylzinc to Aldehydes

Applying aminodiols 6–15 and 19–23 as chiral catalysts in the addition of diethylzinc to benzaldehyde (24), enantiomeric mixture of (S)- and (R)-1-phenyl-1-propanol 25 was obtained (Scheme 7).

The results are presented in Table 2. The enantiomeric excess of 1-phenyl-1-propanols (S)-25 and/or (R)-25 was determined by chiral GC (CHIRASIL-DEX CB column) according to literature methods [65,66]. Low to good enantioselectivities were observed. The results found clearly show that all aminodiols favored the formation of the (R)-enantiomer of 25. In contrast, the application of 20 led to (S)-enantiomer 25 as the main product. Aminodiol 10 and 21 afforded the best ee value (ee = 80%) with an (R)-selectivity, whereas O-benzyl aminodiol 20 showed the best ee value (ee = 74%) with an (S)-selectivity. Moreover, enantioselectivities were also observed in the addition of diethylzinc to benzaldehyde catalyzed by aminodiols 6–8, whereas lower, but still good selectivities were obtained with the use of O-benzyl aminodiol derivatives 19–22. We suppose that the highly rigid structure of O-benzyl aminodiol derivatives in the transition states leads to better selectivities when compared to flexible moieties. Furthermore, our results clearly indicate that the spirooxazolidine ring (ligand 15 and 23) has weaker catalytic performance compared with fused 1,3-oxazine systems [37,38]. These results show good accordance with those observed with sabinane- or pinane-based spirooxazolidines were reported in our earlier studies [40,60].

Table 2. Addition of diethylzinc to benzaldehyde, catalyzed by aminodiol derivatives.

| Entry | Ligand | Yield (%) | ee (%) | Configuration |
|-------|--------|-----------|--------|---------------|
| 1     | 6      | 83        | 5      | (R)           |
| 2     | 7      | 92        | 23     | (R)           |
| 3     | 8      | 80        | 31     | (R)           |
| 4     | 9      | 85        | 4      | (R)           |
| 5     | 10     | 85        | 80     | (R)           |
| 6     | 11     | 90        | 3      | (R)           |
| 7     | 12     | 95        | 16     | (R)           |
| 8     | 13     | 80        | 60     | (R)           |
| 9     | 14     | 83        | –      | –             |
| 10    | 15     | 83        | 26     | (R)           |
| 11    | 16     | 85        | 35     | (R)           |
The best (R)-selectivity can be explained with the steric effect of O-benzyl and N-(S)-1-phenylethyl substituent as it is given on Figure 2. The carbon of ethyl group of EtZn can attack the carbonyl group from the less hindered Re face resulting in (R)-25 as a main product.

![Figure 2. Proposed transition state for the asymmetric addition with 21.](image)

With best catalysts 20 and 21, the diethylzinc addition reaction was extended to further aromatic and aliphatic aldehydes (Scheme 8). Our results are presented in Table 3. The enantiomeric purities of the 1-aryl and 1-alkyl-1-propanols obtained were determined by GC on a CHIRASIL-DEX CB column or by chiral HPLC analysis on a Chiralcel OD-H column, according to the literature methods [37].

![Scheme 8. Model reaction for enantioselective catalysis.](image)
competitive process that takes place without the involvement of the pinane ligand affording racemic product, while the investigated ligand seems to promote the exclusive formation of the $R$-carbinol product.

### Table 3. Addition of diethylzinc to aldehydes, catalyzed by 10 mol % 20 or 21.

| Entry | Catalyst | Products | R                | Yield * (%) | ee $^b$ (%) | Configuration $^c$ |
|-------|----------|----------|------------------|-------------|-------------|-------------------|
| 1     | 20       | 29a      | (4-MeO)C$_6$H$_4$ | 80          | 92          | (S)               |
| 2     | 20       | 29b      | (3-MeO)C$_6$H$_4$ | 78          | 84          | (S)               |
| 3     | 20       | 29c      | (3-Me)C$_6$H$_4$  | 75          | 78          | (S)               |
| 4     | 21       | 29a      | (4-MeO)C$_6$H$_4$ | 83          | 85          | (R)               |
| 5     | 21       | 29b      | (3-MeO)C$_6$H$_4$ | 92          | 87          | (R)               |
| 6     | 21       | 29c      | (3-Me)C$_6$H$_4$  | 80          | 84          | (R)               |
| 7     | 21       | 29d      | cyclohexyl        | 85          | 48          | (R)               |
| 8     | 21       | 29e      | $n$-butyl        | 80          | 45          | (R)               |

$^a$ Are given after silica column chromatography. $^b$ Determined on the crude product by HPLC (Chiracel OD-H) or GC (Chirasil-DEX CB column). $^c$ Determined by comparing the $t_R$ of the HPLC analysis and the optical rotation with the literature data [37].

![Figure 3](image_url) **Figure 3.** Reaction coordinate with activation barrier and thermodynamics of the ethyl transfer connecting complexes 27A and 27C via transition state 27B optimized by the HF/LANL2DZ method.

All calculations were carried out by using Gaussian 09 software package [70]. The optimized structures are available from the authors.

### 3. Discussion

Starting from natural (−)$\beta$-pinene, a monoterpene-based 3-amino-1,2-diol library has been created via the epoxide ring opening of epoxyalcohol as key intermediate, whereas the reactions of $N$-substituted aminodiols with formaldehyde resulted in spirooxazolidines with high regioselectivity. Moreover, O-benzylation of key allylic alcohol intermediate led to O-benzyl aminodiols by aminolysis of its epoxide. The ring closure of O-benzyl, $N$-isopropyl aminodiol furnished the corresponding spirooxazolidine. Aminodiol derivatives were proven reliable chiral catalysts in the enantioselective addition of diethylzinc to aldehydes. The enantioselective nature of the catalytic activity proved to be $N$-substituent-dependent, and molecular modeling was applied to
explain this phenomenon. As a result of the modeling, the O-benzyl and N-(S)-1-phenylethyl substituent aminodiol 21 provided high enantiomeric excess values (80% ee with (R) selectivity) in the model reactions. This ligand also proved to be excellent catalysts in the additions of diethylzinc to either aromatic or aliphatic aldehydes.

4. Materials and Methods

4.1. Materials and General Methods

1H- and 13C- NMR spectra were obtained on a Bruker Avance DRX 500 (Bruker Biospin, Karlsruhe, Baden Württemberg, Germany) [500 and 125 MHz, respectively, δ = 0 ppm (TMS)]. Chemical shifts (δ) are expressed in ppm and related to TMS as internal reference. J values are given in Hz. GC measurements were made on a Perkin-Elmer Autosystem KL GC consisting of a Flame Ionization Detector (Perkin-Elmer Corp., Norwalk, CT, USA) and a Turbochrom Workstation data system (Perkin-Elmer Corporation Norwalk, USA). O-acetyl derivatives of chiral secondary alcohol enantiomers were separated on a CHIRASIL-DEX CB column (2500 mm × 0.265 mm I.D., Agilent Technologies, Inc., Santa Clara, CA, USA). Microanalyses were achieved on a Perkin–Elmer 2400 elemental analyzer (PerkinElmer Inc., Waltham, MA, USA).

Optical rotations were determined with a Perkin–Elmer 341 polarimeter (PerkinElmer Inc., Shelton, CT, USA). Melting points were measured on a Kofler apparatus (Nagema, Dresden, Germany) and the values are uncorrected. Column chromatography of crude products was performed on Merck Kieselgel 60 (230–400 mesh ASTM, Merck Co., Darmstadt, Germany). Headaway of reactions was followed on Merck Kieselgel 60 F254 precoated TLC plates (0.25 mm thickness, Merck Co., Darmstadt, Germany).

(−)-β-Pinene 1 is commercially available from Merck Co (Cat. No.: 402753, Merck Co., Darmstadt, Germany) and its ee value was defined by Merck Co as 97%. The purity of crude products was examined by 1H NMR in each case and we could not observe the presence of any other diastereoisomer in any case. All chemicals and solvents were used as supplied (Molar Chemicals Ltd., Halásztelek, Hungary; Merck Ltd., Budapest, Hungary and VWR International Ltd., Debrecen, Hungary). THF and toluene were dried over Na wire. Synthesis of (−)-nopinone 2 and (−)-3-methylenenopinone 3 were carried out as given in literature procedures, and all physical and chemical properties of 2 and 3 were similar to those described therein [50,51]. All 1H-, 13C- NMR, HMQC, HMBC and NOESY spectra are found in the Supporting Information.

4.2. (1R,2R,5R)-6,6-Dimethyl-3-Methylenebicyclo[3.1.1]heptan-2-ol (4a)

A suspension of CeCl₃·7H₂O (2.46 g, 6.6 mmol) in MeOH (50.0 mL) was added to an ice-cooled solution of 3 (1.0 g, 6.6 mmol) in MeOH (50.0 mL). The reaction mixture was stirred for 30 min before NaBH₄ (0.5 g, 13.2 mmol) was slowly added to the mixture. Stirring was continued for 30 min at 0 °C. When the reaction was complete, the mixture was evaporated at 20 °C then poured into brine and the product was extracted with Et₂O (3 × 150 mL). The combined organic phase was washed with 3.5% HCl aqueous solution (100 mL) and dried (Na₂SO₄). After evaporation of the solvent in vacuo, the crude product 4a was used without further purification for the next step. Yield: 87%, white crystals. m.p.: 51–55 °C. [α]D₂₀ = +78 (c 0.255, MeOH). 1H NMR (500 MHz, CDCl₃): δ = 0.84–0.87 (1H, m), 1.03 (3H, s), 1.25 (3H, s), 1.94–1.95 (1H, m), 2.09–2.12 (1H, m), 2.31–2.36 (1H, m), 2.56–2.77 (2H, m), 4.48 (1H, s), 5.16–5.42 (2H, m). 13C NMR (125 MHz, CDCl₃): δ = 21.7, 27.1, 29.6, 34.4, 38.1, 39.6, 46.4, 75.6, 114.2, 148.6. Anal. Calculated for C₁₀H₁₆O (152.24): C 78.90, H 10.59; found: C 78.95, H 10.57.

4.3. (1R,2R,5R)-6,6-Dimethylspiro[bicyclo[3.1.1]heptane-3,2’-oxiran]-2-ol (5)

To the solution of 4a (1.0 g, 6.6 mmol) in dry toluene (50 ml), catalytic amount of VO(acac)₂ (7.0 mg) was added. The mixture was stirred for 30 min then t-BuOOH (70% solution in water, 1.7 g, 13.2 mmol), dried briefly (Na₂SO₄), was added dropwise at 25 °C. Stirring was continued (20 h) whereupon KOH (2.0 g) in brine (80.0 ml) was added. The mixture was extracted with toluene (3 ×
100 mL), the organic layer was dried (Na₂SO₄) and evaporation at 20 °C gave compound 5 (84%) as yellow oil. Crude product 5 was used for the next step.

4.4. General Procedure for Ring Opening of Epoxide 5 with Primary and Secondary Amines

To a solution of the appropriate amine (1.2 mmol) in MeCN (5.0 mL) and LiClO₄ (0.06 g, 0.6 mmol), solution of epoxide 5 or 18 (0.6 mmol) in MeCN (5.0 mL) was added. After 6 h reflux the reaction was found to be completed (indicated by TLC), and the mixture was evaporated to dryness, the residue was dissolved in water (15.0 mL) and extracted with CH₂Cl₂ (3 × 50 mL). The combined organic phase was dried (Na₂SO₄), filtered and concentrated. The purification of the crude product was accomplished by column chromatography on silica gel with an appropriate solvent mixture resulting in compounds 6–13 or 19–22, respectively.

4.4.1. (1R,2R,3S,5R)-3-((Benzylamino)methyl)-6,6-Dimethylbicyclo[3.1.1]heptane-2,3-diol (6)

Purified by column chromatography on silica gel (n-hexane/EtOAc = 1:2). Yield: 95%, yellow crystals; m.p.: 170–175 °C. [α]D²₀= +7 (c = 0.27, MeOH). ¹H NMR (500 MHz, CDCl₃): δ = 0.80 (1H, d, J = 10.8 Hz), 1.09 (3H, s), 1.20 (3H, s), 1.87–1.90 (2H, m), 2.17–2.23 (3H, m), 2.66 (2H, s), 3.81–3.84 (2H, m), 7.26–7.35 (5H, m). ¹³C NMR (125 MHz, CDCl₃): δ = 21.9, 27.0, 27.5, 37.2, 40.4, 40.6, 47.0, 52.3, 59.7, 66.1, 73.8, 129.1, 129.7, 130.2, 130.2. Anal. Calculated for C₁₇H₂₅NO₂ (275.39): C 74.14, H 9.15, N 5.09; found: C 74.19, H 5.13, N 5.11.

4.4.2. (1R,2S,3S,5R)-6,6-Dimethyl-3-(((R)-1-phenyl-ethyl)amino)methyl)bicyclo[3.1.1]heptane-2,3-diol (7)

Purified by column chromatography on silica gel (n-hexane/EtOAc = 1:2) to Yield: 43%, yellow crystals, m.p.: 112–116 °C. [α]D²₀= +36 (c=0.26, MeOH). ¹H NMR (500 MHz, CDCl₃): δ = 0.76–0.80 (1H, m), 1.07 (3H, s), 1.19 (3H, s), 1.41 (3H, d, J = 6.5 Hz), 1.78–1.86 (2H, m), 2.11–2.22 (3H, m), 2.48 (1H, d, J = 11.4 Hz), 2.60 (1H, d, J = 11.4 Hz), 3.81–3.84 (2H, m), 7.24–7.36 (5H, m). ¹³C NMR (125 MHz, CDCl₃): δ = 21.3, 23.9, 27.3, 27.8, 37.3, 41.0, 41.3, 47.3, 58.1, 62.6, 67.3, 76.5, 126.6, 127.3, 128.7. Anal. Calculated for C₁₈H₂₇NO₂ (289.42): C 74.70, H 9.40, N 4.84; found: C 74.73, H 9.44, N 4.80.

4.4.3. (1R,2S,3S,5R)-6,6-Dimethyl-3-(((S)-1-phenyl-ethyl)amino)methyl)bicyclo[3.1.1]heptane-2,3-diol (8)

Purified by column chromatography on silica gel (n-hexane/EtOAc = 1:2) to Yield: 45%, yellow oil. [α]D²₀= -3 (c = 0.27, MeOH). ¹H NMR (500 MHz, CDCl₃): δ = 0.68 (1H, d, J = 9.1 Hz), 1.08 (3H, s), 1.18 (3H, s), 1.45 (3H, d, J = 6.5 Hz), 1.81–1.86 (2H, m), 2.14–2.20 (3H, m), 2.46–2.48 (1H, d, J = 11.9 Hz), 2.56–2.58 (1H, d, J = 11.9 Hz), 3.75–3.84 (2H, m), 7.24–7.35 (5H, m). ¹³C NMR (125 MHz, CDCl₃): δ = 21.5, 23.7, 27.3, 27.7, 37.3, 41.0, 41.5, 47.2, 58.6, 62.7, 67.3, 76.1, 126.5, 127.3, 128.7. Anal. Calculated for C₁₈H₂₇NO₂ (289.42): C 74.70, H 9.40, N 4.84; found: C 74.73, H 9.44, N 4.80.

4.4.4. (1R,2R,3S,5R)-3-((Disopropylamino)methyl)-6,6-Dimethylbicyclo[3.1.1]heptane-2,3-diol (9)

Purified by column chromatography on silica gel (n-hexane/EtOAc = 1:2) then recrystallized in Et₂O. Yield: 32%, yellow crystals, m.p.: 190–194 °C. [α]D²₀= +8 (c=0.26, MeOH). ¹H NMR (500 MHz, CDCl₃): δ = 0.88 (1H, d, J = 10.7 Hz), 1.04 (3H, s), 1.12 (3H, s), 1.44 (6H, d, J = 6.2 Hz), 1.95–1.97 (2H, m), 2.24–2.35 (3H, m), 3.00 (1H, d, J = 11.9 Hz), 3.12 (1H, d, J = 11.9 Hz), 3.49–3.55 (1H, m), 4.15 (1H, s). ¹³C NMR (125 MHz, CDCl₃): δ = 19.2, 19.4, 22.0, 27.0, 27.5, 37.3, 40.5, 42.0, 47.0, 52.7, 58.7, 66.1, 73.6. Anal. Calculated for C₁₃H₂₅NO₂ (227.35): C 68.68, H 11.08, N 6.16; found: C 68.70, H 11.02, N 6.12.

4.4.5. (1R,2S,3S,5R)-3-((Dibenzylamino)methyl)-6,6-Dimethylbicyclo[3.1.1]heptane-2,3-diol (10)

Purified by column chromatography on silica gel (n-hexane/EtOAc = 9:1). Yield: 40%, yellow oil. [α]D²₀=+16 (c=0.255, MeOH). ¹H NMR (500 MHz, CDCl₃): δ = 0.51 (1H, d, J = 9.2 Hz), 1.06 (3H, s), 1.15 (3H, s), 1.57 (2H, s), 1.80–1.82 (1H, m), 1.90–1.94 (1H, m), 2.08–2.11 (3H, m), 2.63–2.66 (1H, d, J =
13.7 Hz), 2.72–2.75 (1H, d, J = 13.7 Hz), 3.05 (1H, d, J = 6.1 Hz), 3.49 (1H, d, J = 4.0 Hz), 3.74 (4H, s), 3.78–3.80 (1H, m), 4.62 (1H, s), 7.23–7.34 (10H, m). 13C NMR (125 MHz, CDCl3): δ = 12.4, 27.3, 27.8, 37.2, 41.2, 43.1, 47.2, 59.6, 67.9, 68.9, 77.4, 127.3, 128.4, 129.2, 139.0. Anal. Calculated for C22H33NO2 (343.51): C 76.92, H 9.68, N 4.08; found: C 76.88, H 9.71, N 4.13.

4.4.6. (1R,2S,3S,5R)-3-((Benzyl((R)-1-phenylethyl)amino)methyl)-6,6-dimethylbicyclo[3.1.1]heptane-2,3-diol (11)

Purified by chromatography on silica gel column (n-hexane/EtOAc = 9:1). Yield: 30%, white crystals, m.p.: 120–125 °C. [α]D20 = +45 (c = 0.28, MeOH). 1H NMR (500 MHz, CDCl3): δ = 0.49 (1H, d, J = 10.1 Hz), 1.05 (3H, s), 1.14 (3H, s), 1.41–1.42 (3H, d, J = 6.8 Hz), 1.57 (1H, s), 1.82–1.83 (1H, m), 1.98–2.03 (2H, m), 2.08–2.12 (1H, m), 2.15–2.18 (1H, m), 2.48–2.50 (1H, d, J = 13.7 Hz), 2.79 (1H, d, J = 5.7 Hz), 3.55–3.57 (1H, m), 3.77 (2H, s), 4.08–4.12 (1H, m), 4.85 (1H, s), 7.25–7.36 (10H, m). 13C NMR (125 MHz, CDCl3): δ = 13.4, 21.3, 27.3, 28.0, 37.1, 41.3, 43.8, 47.1, 56.0, 57.6, 64.4, 67.3, 77.5, 127.2, 128.2, 128.5, 128.9, 139.7, 141.9. Anal. Calculated for C22H33NO2 (379.54): C 79.11, H 8.76, N 3.69; found: C 79.08, H 8.81, N 3.65.

4.4.7. (1R,2S,3S,5R)-3-((Benzyl((S)-1-phenylethyl)amino)methyl)-6,6-dimethylbicyclo[3.1.1]heptane-2,3-diol (12)

Purified by column chromatography on silica gel column (n-hexane/EtOAc = 9:1). Yield: 60%, yellow oil. [α]D20 = –28 (c=0.26, MeOH). 1H NMR (500 MHz, CDCl3): δ = 0.62–0.65 (1H, m), 1.05 (3H, s), 1.15 (3H, s), 1.42 (3H, d, J = 6.3 Hz), 1.76–1.79 (1H, m), 1.81–1.85 (1H, m), 1.99–2.03 (1H, m), 1.15–2.18 (2H, m), 2.58 (1H, d, J = 14.2 Hz), 2.79 (1H, d, J = 13.8 Hz), 3.66–3.68 (1H, d, J = 12.8 Hz), 3.82–3.85 (1H, d, J = 13.6 Hz), 3.86 (1H, s), 5.29 (1H, s), 7.24–7.35 (10H, m). 13C NMR (125 MHz, CDCl3): δ = 12.7, 21.3, 27.3, 28.2, 37.0, 41.1, 43.8, 47.2, 55.4, 57.3, 65.0, 66.8, 78.3, 127.2, 127.3, 128.2, 128.5, 128.9, 139.4, 142.0. Anal. Calculated for C22H33NO2 (379.54): C 79.11, H 8.76, N 3.69; found: C 79.08, H 8.81, N 3.65.

4.4.8. (1R,2S,3S,5R)-3-((4-Benzylpiperidin-1-yl)methyl)-6,6-dimethylbicyclo[3.1.1]heptane-2,3-diol (13)

Purified by column chromatography on silica gel (n-hexane/EtOAc = 1:1). Yield: 55%, yellow oil. [α]D20 = +14 (c = 0.26, MeOH). 1H NMR (500 MHz, CDCl3): δ = 0.75 (1H, d, J = 9.6 Hz), 1.10 (3H, s), 1.19 (3H, s), 1.25–1.33 (2H, m), 1.51–1.63 (4H, m), 1.85–1.89 (1H, m), 1.91–1.95 (1H, m), 2.17–2.28 (5H, m), 2.48–2.56 (4H, m), 2.89–3.01 (2H, m), 3.68–3.76 (2H, m), 7.12–7.28 (5H, m). 13C NMR (125 MHz, CDCl3): δ = 21.2, 27.5, 28.4, 32.4, 41.2, 43.1, 44.6, 47.1, 54.3, 55.5, 74.4, 152.8, 128.2, 129.1, 131.7. Anal. Calculated for C25H33NO2 (393.51): C 76.92, H 9.68, N 4.08; found: C 76.88, H 9.71, N 4.13.

4.4.9. (1R,2S,3S,5R)-3-((Benzylamino)methyl)-2-(benzyloxy)-6,6-dimethylbicyclo[3.1.1]heptan-3-ol (19)

Purified by column chromatography on silica gel (n-hexane/EtOAc = 1:2). Yield: 32%, yellow oil. [α]D20 = +35 (c = 0.27, MeOH). 1H NMR (500 MHz, CDCl3): δ = 0.95 (3H, s), 1.23 (3H, s), 1.79 (2H, d, J = 10.1 Hz), 1.90–1.92 (3H, m), 2.16–2.24 (2H, m), 2.42–2.45 (1H, m), 3.31 (1H, d, J = 11.8 Hz), 3.69 (1H, d, J = 13.1 Hz), 3.77 (1H, d, J = 13.5 Hz), 3.87 (1H, d, J = 4.6 Hz), 4.21 (1H, d, J = 10.5 Hz), 4.59 (1H, d, J = 11.4 Hz), 7.10–7.12 (2H, m), 7.20–7.32 (5H, m). 13C NMR (125 MHz, CDCl3): δ = 22.2, 24.7, 27.3, 37.5, 38.9, 40.0, 41.2, 54.2, 56.7, 70.0, 71.4, 89.2, 126.9, 127.4, 127.9, 128.4, 138.8. Anal. Calculated for C28H35NO2 (365.52): C 78.86, H 8.55, N 3.83; found: C 78.90, H 8.51, N 3.80.

4.4.10. (1R,2S,3S,5R)-2-(Benzyloxy)-6,6-dimethyl-3-(((R)-1-phenylethyl)amino)methyl)bicyclo[3.1.1]heptan-3-ol (20)

Purified by column chromatography on silica gel (n-hexane/EtOAc = 1:2). Yield: 36%, white crystals, m.p.: 84–86 °C. [α]D20 = +4 (c = 0.26, MeOH). 1H NMR (500 MHz, CDCl3): δ = 0.89 (3H, s), 1.22 (3H, s), 1.24 (3H, d, J = 6.1 Hz), 1.79 (1H, d, J = 10.0 Hz), 1.84–1.90 (3H, m), 2.01 (1H, d, J = 10.6 Hz), 2.17–2.22 (1H, m), 2.43–2.46 (1H, dd, J = 4.6 Hz, 11.6 Hz), 3.03 (1H, d, J = 11.5 Hz), 3.61 (1H, dd, J = 6.7 Hz).
Hz, 13.5 Hz), 3.89 (1H, d, J = 4.3 Hz), 4.19 (1H, d, J = 11.6 Hz), 4.60 (1H, d, J = 10.3 Hz), 6.88–6.90 (2H, m), 7.16–7.19 (3H, m), 7.25–7.37 (5H, m). 13C NMR (125 MHz, CDCl3): δ = 22.2, 24.5, 34.8, 27.3, 37.5, 38.8, 40.0, 47.2, 41.1, 55.3, 58.9, 70.2, 71.3, 89.5, 126.0, 126.6, 127.6, 127.9, 128.4, 128.5. Anal. Calculated for C25H33NO2 (379.25): C 79.11, H 8.76, N 3.69; found: C 79.10, H 8.80, N 3.73.

4.4.11. (1R,2S,3S,5R)-2-(Benzyloxy)-6,6-dimethyl-3-(((S)-1-phenylethyl)amino)methyl)bicyclo[3.1.1]heptan-3-ol (21)

Purified by column chromatography on silica gel (n-hexane/EtOAc = 1:2). Yield: 30%, yellow oil. [α]D20 = −10 (c = 0.28, MeOH). 1H NMR (500 MHz, DMSO-d6): δ = 0.87 (3H, s), 1.04 (3H, s), 1.16 (3H, d, J = 7.0 Hz), 1.22 (3H, s), 1.75 (1H, d, J = 10.1 Hz), 1.81–1.83 (2H, m), 1.86–1.88 (1H, m), 2.10 (1H, d, J = 11.2 Hz), 2.16–2.20 (1H, m), 2.44 (1H, q, J = 4.9 Hz, 11.0 Hz), 3.21 (1H, d, J = 11.0 Hz), 3.70 (1H, dd, J = 6.3 Hz, 13.4 Hz), 3.90 (1H, d, J = 4.2 Hz), 4.26 (1H, d, J = 11.5 Hz), 4.63 (1H, d, J = 11.5 Hz), 7.19–7.38 (10H, m). 13C NMR (125 MHz, DMSO-d6): δ = 22.2, 24.2, 24.7, 27.3, 37.5, 38.9, 40.0, 41.3, 54.7, 57.9, 70.1, 71.3, 89.5, 126.7, 126.9, 127.4, 127.5, 128.4, 128.4. Anal. Calculated for C25H33NO2 (379.25): C 79.11, H 8.76, N 3.69; found: C 79.08, H 8.71, N 3.74.

4.4.12. (1R,2S,3S,5R)-2-(Benzyloxy)-3-(((isopropylamino)methyl)-6,6-dimethylbicyclo[3.1.1]heptan-3-ol (22)

Purified by column chromatography on silica gel (n-hexane/EtOAc = 1:9) then recrystallized from EtO. Yield: 36%, yellow crystals, m.p.: 176–179 °C. [α]D20 = +33 (c = 0.26, MeOH). 1H NMR (500 MHz, CDCl3): δ = 0.87 (3H, d, J = 6.1 Hz), 1.04 (3H, s), 1.16 (3H, d, J = 7.0 Hz), 1.30 (3H, s), 1.74 (1H, d, J = 10.3 Hz), 2.01–2.03 (1H, m), 2.07–2.16 (2H, m), 2.25–2.30 (1H, m), 2.62 (1H, dd, J = 4.9 Hz, 6.0 Hz), 3.13–3.23 (2H, m), 3.30–3.34 (1H, m), 4.28 (1H, d, J = 4.2 Hz), 4.41 (1H, d, J = 8.8 Hz), 4.56 (1H, d, J = 9.3 Hz), 6.40 (1H, s), 6.83 (1H, s), 7.29–7.43 (5H, m). 13C NMR (125 MHz, CDCl3): δ = 18.4, 19.4, 22.2, 24.4, 27.0, 37.1, 39.6, 39.8, 40.7, 51.9, 52.7, 69.8, 71.1, 85.8, 128.4, 128.7, 129.2, 137.4. Anal. Calculated for C32H31NO2 (474.11): C 75.67, H 9.84, N 4.41; found: C 75.70, H 9.81, N 4.46.

4.5. (1R,2R,3S,5R)-3-(Aminomethyl)-6,6-dimethylbicyclo[3.1.1]heptane-2,3-diol (14)

To a suspension of 5% Pd/C (87 mg) in n-hexane/EtOAc = 1:2 (20 mL) was added n-hexamethylenemine dibromide (0.29 g, 1.0 mmol) dissolved in n-hexane/EtOAc = 1:2 (20 mL). The mixture was stirred under a hydrogen atmosphere at 25 °C. The reaction was monitored by means of TLC and was completed after 24 h stirring at room temperature. The resulting mixture was filtered through a Celite pad and the solution was evaporated to dryness. The obtained crude product was recrystallized in Et2O, resulting in primary aminodiol 14 as the single product.

Yield: 74%, yellow crystals, m.p.: 204–207 °C. [α]D20 = +10 (c = 0.27, MeOH). 1H NMR (500 MHz, DMSO-d6): δ = 0.90 (1H, d, J = 10.5 Hz), 1.03 (3H, s), 1.17 (3H, s), 1.93–2.03 (2H, m), 2.08–2.09 (1H, m), 2.19–2.24 (1H, m), 2.72 (1H, d, J = 12.6 Hz), 2.83 (1H, d, J = 12.5 Hz), 3.74 (1H, s), 4.78 (1H, s), 5.69 (1H, s). 13C NMR (125 MHz, DMSO-d6): δ = 22.4, 27.6, 27.7, 37.3, 41.0, 47.1, 53.4, 66.2, 73.8. Anal. Calculated for C10H19NO2 (185.27): C 64.83, H 10.34, N 7.56; found: C 64.80, H 10.31, N 7.61.

4.6. General Procedure for Ring Closure of Aminodiol Derivatives with Formaldehyde

To the solution of aminodiolis 6, 9 or 22 (1.8 mmol) in EtO (5 mL), 35% aqueous formaldehyde (20 mL) was added in one portion. The mixture was stirred at room temperature for 1 h, then made alkaline with 10% aqueous KOH (20 mL) and extracted with EtO (3 × 50 mL). After drying (Na2SO4) and solvent evaporation, crude products 15, 16 or 23 were purified by column chromatography with an appropriate solvent mixture.

4.6.1. (1R,2S,3S,5R)-3’-Benzy1-6,6-dimethylspiro[bicyclo[3.1.1]heptane-3,5’-oxazolidin]-2-ol (15)

Purified by column chromatography on silica gel (n-hexane/EtOAc = 2:1). Yield: 98%, yellow oil. [α]D20 = +8 (c = 0.25, MeOH). 1H NMR (500 MHz, DMSO-d6): δ = 0.80 (1H, d, J = 10.3 Hz), 1.01 (3H, s), 1.14 (3H, s), 1.78–1.82 (1H, m), 2.01–2.04 (1H, m), 2.12–2.23 (3H, m), 2.83 (1H, d, J = 10.4 Hz), 2.92 (1H,
d, \( J = 9.8 \) Hz), 3.74 (2H, s), 3.82 (1H, \( J = 3.6 \) Hz), 3.89 (1H, d, \( J = 3.6 \) Hz), 4.25 (1H, d, \( J = 3.4 \) Hz), 4.32 (1H, d, \( J = 3.4 \) Hz), 7.23–7.35 (5H, m). \(^{13}\)C NMR (125 MHz, DMSO-d6): \( \delta = 22.3, 27.1, 27.5, 37.1, 40.2, 42.5, 46.3, 56.5, 71.9, 78.0, 79.2, 86.3, 127.4, 128.8, 139.4 \). Anal. Calculated for C\(_{18}\)H\(_{25}\)NO\(_2\) (287.19): C 75.22, H 8.77, N 4.87; found: C 75.21, H 8.80, N 4.82.

4.6.2. (1\(R\),5\(R\))-3'-Isopropyl-6,6-dimethylspiro[bicyclo[3.1.1]heptane-3,5'-oxazolidin]-2-ol (16)

Purified by column chromatography on silica gel (n-hexane/EtOAc = 1:9). Yield: 40%, yellow oil. \([\alpha]_D^{20} = +6 \) (c = 0.255, MeOH). \(^{1}H\) NMR (500 MHz, DMSO-d6): \( \delta = 0.89-0.91 \) (1H, d, \( J = 10.4 \) Hz), 0.98 (3H, s), 1.01-1.04 (6H, dd, \( J = 6.14 \) Hz), 1.15 (3H, s), 1.78–1.81 (1H, m), 2.00–2.03 (1H, m), 2.09–2.19 (3H, m), 2.47 (1H, s), 2.64-2.68 (1H, m), 2.85-2.86 (1H, m), 1.32-1.37 (1H, m), 4.20 (1H, d, \( J = 4.34 \) Hz). \(^{13}\)C NMR (125 MHz, DMSO-d6): \( \delta = 22.2, 22.3, 26.9, 27.5, 37.3, 41.6, 46.3, 51.9, 69.4, 78.6, 78.9, 85.2 \). Anal. Calculated for C\(_{14}\)H\(_{25}\)NO\(_2\) (239.36): C 70.25, H 10.53, N 5.85; found: C 70.28, H 10.50, N 5.89.

4.6.3. (1\(R\),2\(S\),3\(S\),5\(R\))-2-(Benzyloxy)-3'-isopropyl-6,6-dimethylspiro[bicyclo[3.1.1]heptane-3,5'-oxazolidine] (23)

Purified by column chromatography on silica gel (n-hexane/EtOAc = 4:1). Yield: 50%, yellow oil. \([\alpha]_D^{20} = +32 \) (c = 0.23, MeOH). \(^{1}H\) NMR (500 MHz, CDCl3): \( \delta = 0.94 (3H, s), 1.05 (6 \) H, d, \( J = 7.0 \) Hz), 1.22 (3H, s), 1.54 (1H, d, \( J = 10.0 \) Hz), 1.87–1.91 (1H, m), 2.16–2.23 (3H, m), 2.29–2.32 (1H, m), 2.43–2.48 (2H, m), 3.78−3.81 (2H, m), 4.24 (1H, d, \( J = 4.0 \) Hz), 4.46 (1H, d, \( J = 11.9 \) Hz), 4.62 (1H, d, \( J = 11.7 \) Hz), 7.23–7.35 (5H, m). \(^{13}\)C NMR (125 MHz, CDCl3): \( \delta = 22.0, 22.2, 22.3, 26.9, 27.5, 37.5, 39.9, 40.6, 42.7, 52.2, 58.6, 71.6, 82.5, 84.0, 87.8, 127.1, 127.2, 128.1, 139.3 \). Anal. Calculated for C\(_{21}\)H\(_{31}\)NO\(_2\) (329.48): C 76.55, H 9.48, N 4.25; found: C 76.51, H 9.50, N 4.27.

4.7. (1\(R\),2\(S\),5\(R\))-2-(Benzyloxy)-6,6-dimethyl-3-methylenebicyclo[3.1.1]heptane (17)

A suspension of NaH (60% purity, 0.26 g, 6.6 mmol) in dry THF (10.0 mL) was added to a solution of 3 (1.0 g, 6.6 mmol) in dry THF (20.0 mL). The reaction mixture was stirred at 25 °C for 30 min than KI (1.1 g, 6.6 mmol) and benzyl bromide (1.2 mL, 13.2 mmol) were added to the suspension. After stirring for 6 h at 60 °C the reaction was completed (monitored by means of TLC) and the mixture was poured into saturated NH\(_4\)Cl solution (30 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phase was dried over anhydrous Na\(_2\)SO\(_4\). The solvent was evaporated in vacuo and the crude product \(17\) was used for the next step.

4.8. (1\(R\),2\(S\),3\(S\),5\(R\))-2-(Benzyloxy)-6,6-dimethylspiro[bicyclo[3.1.1]heptane-3,2'-oxirane] (18)

To a mixture of solution of 17 (0.4 g, 1.65 mmol) in CH\(_2\)Cl\(_2\) (20 mL) and Na\(_2\)HPO\(_4\)·2H\(_2\)O (0.88 g, 4.95 mmol) in water (20 mL), m-chloroperbenzoic acid (70% purity, 0.81 g, 3.3 mmol) was added at 0 °C. The reaction was completed after 2 h stirring at 25 °C (indicated by means of TLC), then the mixture was separated and the aqueous phase was extracted with CH\(_2\)Cl\(_2\) (3 × 50 mL). The organic layer was washed with a 5% KOH solution (3 × 20 mL), then dried (Na\(_2\)SO\(_4\)) and evaporated in vacuo. The crude product was purified by column chromatography on silica gel (n-hexane/EtOAc = 19:1) to provide 20 as the single product.

Yield: 47%, colorless oil. \([\alpha]_D^{20} = +48 \) (c = 0.26, MeOH). \(^{1}H\) NMR (500 MHz, CDCl3): \( \delta = 1.10 (3H, s), 1.19–1.22 (1H, m), 1.24–1.26 (1H, m), 1.27 (3H, s), 1.34–1.35 (1H, m), 1.90 (1H, dd, \( J = 3.6 \) Hz, \( J = 10.9 \) Hz), 2.01–2.04 (1H, m), 2.36–2.42 (3H, m), 2.69 (1H, d, \( J = 6.0 \) Hz), 3.32 (1H, d, \( J = 5.4 \) Hz), 3.75 (1H, d, \( J = 2.5 \) Hz), 4.34 (1H, d, \( J = 12.3 \) Hz), 4.56 (1H, d, \( J = 11.4 \) Hz), 7.25–7.34 (5H, m). \(^{13}\)C NMR (125 MHz, CDCl3): \( \delta = 22.5, 26.8, 28.4, 36.0, 37.3, 40.8, 42.9, 53.3, 58.4, 71.0, 85.0, 127.3, 127.4, 128.3, 138.8 \). Anal. Calculated for C\(_{14}\)H\(_{22}\)O\(_2\) (258.36): C 79.03, H 8.58; found: C 79.07, H 8.61.

4.9. General Procedure for the Reaction of Diethylzinc with Aldehydes in the Presence of Chiral Catalysts

The mixture of appropriate catalyst (0.15 mmol) and 1 M Et\(_2\)Zn in n-hexane solution (1.5 mL, 1.5 mmol) was stirred for 25 min in argon atmosphere at room temperature and then appropriate aldehyde (1.5 mmol) was added to the mixture in one portion. After 20 h of stirring at room
temperature, the reaction was quenched with saturated NH₄Cl solution (15 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layer was washed with H₂O (10 mL) and dried (Na₂SO₄) and the solvent was evaporated under vacuum resulting in 25 and 29a−e. The ee and absolute configuration of the resulting phenyl-1-propanol (25) were determined by chiral GC on a Chirasil-DEX CB column after O-acetylation in Ac₂O/DMPA/pyridine [65,66] and without derivatization for 1-cyclohexyl-1-propanol (29d) and 3-heptanol (29e) [37]. Identification of 29a−c was done by chiral HPLC analysis on a Chiralcel OD-H column with V(n-hexane)/V(2-propanol) = 98:2 mixture, 1.0 mL/min, 210 nm and the direction of the optical rotation of products was also checked [37].

Supplementary Materials: The following are available online at www.mdpi.com/2073-4344/10/5/474/s1, ¹H-, ¹³C- NMR, HMQC, HMBC and NOESY spectra of new compounds as Figure S3–S83.

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