Article

Stereoselective Syntheses and Application of Chiral Bi- and Tridentate Ligands Derived from (+)-Sabinol

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Abstract: A library of bidentate diols, as well as tridentate triols and aminodiols, derived from (+)-sabinol, was synthesized in a stereoselective manner. Sabinol was transformed into allylic trichloroacetamide via Overman rearrangement of the corresponding trichloroacetimidate. After changing the protecting group to Boc, the enamine was subjected to stereospecific dihydroxylation with OsO₄/NMO, resulting in the (1R,2R,3R,5R)-aminodiol diastereomer. The obtained primary aminodiol was transformed to a secondary analogue. The ring closure of the N-benzyl-substituted aminodiol with formaldehyde was investigated and regioselective formation of the spiro-oxazolidine ring was observed. Hydroboration or dihydroxylation of sabinol or its benzyl ether with OsO₄/NMO resulted in the formation of sabinane-based diols and triols following a highly stereospecific reaction. Treatment of sabinol with m-CPBA afforded O-benzoyl triol as a diastereoisomer of the directly dihydroxylated product, instead of the expected epoxy alcohol. The resulting aminodiols, diol, and triols were applied as chiral catalysts in the reaction of diethylzinc and benzaldehyde from moderate to good selectivity.

Keywords: sabinol; terpenoid; catalyst; chiral ligand; triol; aminodiol; asymmetric catalysis

1. Introduction

In recent years, the discovery and application of new chiral auxiliaries and catalysts have become a crucial question in stereoselective syntheses [1–4]. To achieve new, efficient, and commercially available chiral catalysts, natural chiral terpenes [5], including (+)-pulegone [6–8], α- and β-pinene [9–14], and fenchone-camphor [15–19] have proved to be excellent sources. Starting from these readily available natural sources, several powerful chiral catalysts, including various di- and trifunctional synths, such as 1,3-aminoalcohols and aminodiols, have been applied in stereoselective syntheses [5,20].

Besides their importance in enantioselective catalysis, 3-amino-1,2-diols are good starting materials for the synthesis of various heterocyclic ring systems, such as 1,3-oxazines or oxazolidines [8,11,21–25]. Several mono- or bicyclic aminodiol derivatives possess remarkable biological activity.
The Abbott aminodiol was also found to be a useful building block for the synthesis of the potent renin inhibitor Zankiren [26]. Some 3-amino-1,2-diols have been investigated as selective antagonists on receptor P2X1 [27]. Cytokaxone is a naturally occurring heterocyclic aminodiol derivative isolated from Streptomyces species [28,29], and expresses cytokine modulator activity by inhibiting the signaling pathway of Th2 cells [30,31]. Some bicyclic aminodiol-based carbocyclic nucleoside analogues exert antiviral activity [32].

Monoterpene-based diols or triols have also proved to be easily available, good chiral auxiliaries and catalysts [33,34]. Some of the terpenoid diols also possess marked biological, e.g., antimicrobial, antifungal or enzyme inhibitor activities [35–37].

Similar to pinane- and carane-based allylic alcohols, (+)-sabinol and its acetate are available from the essential oil of several plants e.g., Juniperus sabina L. in a large scale [38–40]. Although this interesting monoterpene derivative has been intensively studied from the biological point of view, it was scarcely investigated for its chemical transformations [41].

Our present aim was to synthesize a library of sabinane-based chiral di- and trifunctional synthons, such as 3-amino-1,2-diols, diols, and triols starting from (+)-sabinol, achieved from a natural source. We also decided to evaluate the resulting synthons as catalysts in the asymmetric addition of Et2Zn to benzaldehyde. The planned aminodiols, diols, and triols may serve as useful building blocks for the synthesis of new heterocyclic ring systems and biologically active compounds.

2. Results

2.1. Synthesis and Transformations of Sabinol-Based 3-Amino-1,2-Diols

(+)-Sabinol 1, the key starting material, was isolated from the essential oil of Juniperus sabina L. according to the literature procedure, and its purity was found to be >98% based on GC analysis [38–40].

Sabinol was transformed into trichloroacetimidate 2 in the presence of trichloroacetonitrile and DBU as a strong base (Scheme 1) [8,11]. 2 underwent Overman rearrangement by heating in the presence of K2CO3, resulting in protected allylamine 3 [42]. Since we have found difficulties during the deprotection of N-trichloroacetyl aminodiols in our recent studies [8], we have changed the protecting group to Boc in a two-step process via enamine 4. Stereospecific dihydroxylation of 5, applying OsO4 as the catalyst and NMO as the oxidant, produced protected (1R,2R,3R,5R)-aminodiol 6 as a single diastereomer (based on the 1H NMR study of the crude product). Acid-catalyzed removal of the protecting group resulted in primary aminodiol hydrochloride 7 with 41% overall yield.

Scheme 1. Reagents and conditions: (i) CCl3CN, DBU, dry CH2Cl2, rt, 2 h; (ii) anhydrous K2CO3, dry xylene, reflux, 12 h, 77%; (iii) 2 N aq NaOH, EtOH, rt, 2 h, 72%; (iv) Boc2O, TEA, DMAP, THF, rt, 22 h, 95%; (v) OsO4, NMO, acetone/H2O, rt, 12 h, 93%; (vi) 5% aq HCl, Et2O, rt, 24 h, 77%; (vii) 15% aq KOH, CH2Cl2, rt, 83%.
The relative configuration of 6 was determined by NOESY spectral analysis. Clear NOE correlations were observed between Me of the isopropyl group at position 5 and H-1, OH-2, as well as between H-6 and H-3, CH₂NHBoc. Therefore, the structure of 6 was assigned as shown in Figure 1.

Aminodiol 8 was transformed to N-benzyl derivative 9 by reductive alkylation via condensation with benzaldehyde, followed by subsequent reduction with sodium borohydride (Scheme 2). Next, the regioslectivity of the ring closure of 9 with formaldehyde was investigated. The reaction has proved to be highly regioselective, resulting only in spiro-oxazolidine 10, while the fused 1,3-oxazine structure could not be detected from the crude product by means of ¹H NMR spectroscopy. This observation shows similarity with earlier results we have obtained after ring closure of pinane-based 3-amino-1,2-diols [23], and it is in contrast with those of carane-based analogues [24,25].

Since monoterpenic diols and triols might serve as chiral catalysts or could be used as excellent starting materials for the synthesis of more complex 1,3-heterocycles [34,43], we decided to explore the preparation and some transformations of sabinane-based diols and triols starting from (+)-sabinol 1.

Hydroboration reaction of 1 with BH₃·THF or BH₃·Me₂S followed by treatment with H₂O₂ resulted in cis bicyclic diol 11 in a highly stereospecific reaction (Scheme 3). Beside the NOESY spectral structural analysis, the relative configuration of 11 was determined by X-ray crystallography (Figure 2).
The planes of the two rings in 11 make an angle of 76.90(14)°. The cyclopentane ring has an envelope conformation with atom C1 as the tip. The substituent O6–H6 occupies an axial position on the envelope tip, whereas the isopropyl and O8–H8 substituents are in equatorial positions. In the crystal packing, both hydroxyl groups are involved in hydrogen bonds [O6…O8(−1/2 + x, −1/2 − y, 1 − z) = 2.6796(18) Å, O8…O6(1 + x, y, z) = 2.7223(16) Å], resulting in a double chain of molecules running in the a-axis direction (Figure S1).

Figure 2. Crystal structure of compound 11. Thermal ellipsoids are drawn at the 50% probability level.

The synthesis of sabinane-based triols also started from 1. (+)-Sabinol was treated with the OsO₄/NMO system providing triol 13 in a highly stereospecific reaction. In order to compare the catalytic importance of hydroxyl functions, O-benzyl derivative 14 was also prepared via benzylation of 1 with benzyl bromide, followed by stereospecific dihydroxylation (Scheme 4).

Scheme 4. (i) BnBr, NaH, THF, reflux, 1 h, 92%; (ii) OsO₄, NMO, acetone/H₂O, rt, 12 h, 44%; (iii) OsO₄, NMO, acetone/H₂O, rt, 12 h, 81%.

Treatment of sabinol 1 with m-CPBA did not yield the desired epoxide 15. Rather, the generated epoxide underwent an in situ ring-opening process after the electrophilic attack of the formed m-chlorobenzoic acid, resulting in ester 17 (Scheme 5) [44–46]. The intermediate epoxide could not be isolated even after applying miscellaneous conditions, such as varying temperature, NaHCO₃ or Na₂CO₃, or buffer solutions. 17 easily underwent acyl migration under the applied conditions, affording its structural isomer 18. Interesting to note that while under slightly alkaline work up conditions (sat. NaHCO₃ solution) only isomer 18 was isolated, applying strong alkaline conditions (10% NaOH solution), the mixture of two regioisomers was isolated. Acyl migration of the pure products could also be observed during 13C NMR analysis in CDCl₃ solution. It must be mentioned that Garside et al. reported a similar reaction of sabinol with peracetic acid; however, they observed ring rearrangement and formation of acetyl p-menthane-1,2,4-triol [47].
Scheme 5. (i) m-CPBA, CH₂Cl₂, Na₂HPO₄ buffer sol. (pH = 9.2), rt, 1 h, work up with 10% NaOH/H₂O, 37% (mixture of 17 and 18); (ii) m-CPBA, CH₂Cl₂, Na₂HPO₄ buffer sol. (pH = 9.2), rt, 1 h, work up with sat. NaHCO₃/H₂O, 38% (18); (iii) 10% NaOH/H₂O, EtOH, rt, 30 min, 91%.

The regioisomeric relation of 17 and 18 was determined by their hydrolysis under alkaline conditions, which furnished stereohomogenic compound 19, whereas the relative configuration of 19 was assigned by NOESY spectral structural analysis and 19 was found to be a diastereoisomer of triol 13.

2.3. Application of Sabinol-Based Aminodiol, Diol and Triol Derivatives as Chiral Ligands in the Enantioselective Addition of Diethylzinc to Benzaldehyde

Application of the prepared 3-amino-1,2-diols (8–10), 1,3-diol (11), and triols (13, 14 and 17–19) as catalysts in the ethylation of benzaldehyde resulted in 1-phenyl-1-propanol enantiomers 21 and 22 (Scheme 6).

Scheme 6. Catalyzed addition of diethylzinc to benzaldehyde.

The enantiomeric purity of the secondary alcohol obtained was determined by HPLC analysis [7]. Catalysts were applied in 10% molar ratio and reactions were carried out in n-hexane at room temperature. The results are presented in Table 1.
Table 1. Addition of diethylzinc to benzaldehyde, catalyzed by various types of diol, triols, and aminodiols at room temperature.

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<tr>
<th>Entry</th>
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1 Yields after silica column chromatography. 2 Determined on the crude product by HPLC (Chiracel OD-H). 3 Determined by comparing the tR of the HPLC analysis and the optical rotation with the literature data [7].

In the addition of Et2Zn in n-hexane solution to benzaldehyde, diol 11, or triols 13, 14, and 17–19 afforded the corresponding alcohols with low enantioselectivities. The stereoselectivity could not be improved either by changing the solvent to toluene or lowering the reaction temperature. Increased, but still moderate asymmetric induction was observed when aminodiol derivatives 8–10 were used. The formation of S enantiomer 22 was predominant in all cases.

3. Experimental Section

3.1. Materials and Methods

1H and 13C NMR spectra were recorded on a Bruker Avance DRX 300 and 500 spectrometer [δ = 0 (TMS)] (Bruker Corp., Billerica, MA, USA) in the solvents indicated. Chemical shifts are expressed in ppm (δ) relative to TMS as internal reference. J values are given in Hz. Elemental analyses were performed on a Perkin-Elmer 2400 Elemental Analyzer (PerkinElmer Inc., Waltham, MA, USA). Chiral HPLC analysis was performed without derivatization by JASCO LC-4000 system on a Chiralcel OD-H column (250 × 4.6 mm, Jasco Europe S.R.L., Cremella, Italy). UV detection was monitored at 215 nm. Optical rotations were obtained with a Perkin-Elmer 341 polarimeter (PerkinElmer Inc., Shelton, CT, USA). Melting points were determined on a Kofler apparatus (Nagema, Dresden, Germany) and are uncorrected. Chromatographic separations were carried out on Merck Kieselgel 60 (230–400 mesh ASTM, Merck Ltd., Budapest, Hungary). Reactions were monitored with Merck Kieselgel 60 F254-precoated TLC plates (0.25 mm thickness). All chemicals and solvents were used as supplied.

Sabinol 1 was isolated from the essential oil of Juniperus sabina L. according to a literature process [38–40].

Synthesis of 2,2,2-Trichloro-N-(((1R,5S)-5-Isopropylbicyclo[3.1.0]Hex-2-En-2-Yl)Methyl)Acetamide (3). To a solution of sabinol 1 (4.00 g, 26.27 mmol) in dry CH2Cl2 (50 mL) 1,8-diazabicycloundecene-7-ene (2 mL, 13.39 mmol) and CCl3CN (4.68 mL, 46.67 mmol) were added at 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred for 2 h. When the reaction was completed (monitored by means of TLC), the mixture was concentrated to a volume of 20 mL and then filtered through a short pad of silica gel, washing with CH2Cl2. Evaporation of the solvent in vacuum gave a brown oil, which was immediately dissolved in dry xylene (200 mL). To this solution, anhydrous K2CO3 (1.00 g, 7.23 mmol) was added, and the mixture was treated at reflux temperature overnight. The obtained solution was then filtered through a Celite pad, washed, and concentrated under reduced pressure. The obtained crude product was purified by column chromatography on silica gel (Rf = 0.52; n-hexane/EtOAc = 9/1).
Compound 3: 6.03 g (77%); pale-yellow crystalline powder; mp: 45–47 °C; [α]20D = +7 (c = 0.250; MeOH). 1H NMR (300 MHz, CDCl3) δ (ppm): 0.08 (1H, t, J = 3.4 Hz), 0.84 (1H, dd, J = 3.8, 7.5 Hz), 0.90 (3H, d, J = 6.9 Hz), 0.95 (3H, d, J = 6.8 Hz), 1.39–1.52 (2H, m), 2.25 (1H, d, J = 17.7 Hz), 2.45 (1H, dd, J = 2.2, 17.7 Hz), 3.98–4.16 (2H, m), 5.26 (1H, s), 6.79 (1H, br s). 13C NMR (75 MHz, CDCl3) δ (ppm): 19.9, 20.2, 21.8, 28.4, 32.8, 34.0, 36.4, 41.8, 92.9, 124.0, 144.1, 161.8. Anal. Calcld for C13H16ClNO: C 48.59; H 5.44; Cl 35.86; N 4.72. Found: C 48.65; H 5.52; Cl 35.63; N 4.68.

**Synthesis of ((1R,5S)-5-Isopropylbicyclo[3.1.0]Hex-2-En-2-Yl)Methanamine (4).** A solution of acetamide 3 (5.95 g, 20 mmol) in ethanol (30 mL) was stirred with 2 N aqueous NaOH solution (30 mL) at room temperature for 2 h. The reaction mixture was then concentrated to an aqueous residue which was extracted with CH2Cl2 (3 × 30 mL). The organic layer was dried (Na2SO4) and evaporated to dryness. Compound 4 was used without further purification.

**Synthesis of Tert-Butyl ((1R,5S)-5-Isopropylbicyclo[3.1.0]Hex-2-En-2-Yl)Methyl Carbamate (5).** To a solution of 4 (2.00 g, 13.22 mmol) TEA (3.34 g, 33.05 mmol), DMAP (0.16 g, 1.32 mmol) in THF (100 mL) and BocO (3.17 g, 14.54 mmol) were added at room temperature. The reaction mixture was stirred for 22 h and then concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (Rf = 0.50; n-hexane/EtOAc = 9/1).

**Synthesis of Tert-Butyl (((1R,2R,3R,5R)-2,3-Dihydroxy-5-Isopropylbicyclo[3.1.0]Hexan-2-Yl)Methyl)Carbamate (6).** To 5 (3.00 g, 11.93 mmol) in acetone (50 mL) 4-methylmorpholine N-oxide (10 mL, 50% aqueous solution) and OsO4 (4 mL, 2% tert-ButOH solution) were added. The reaction mixture was stirred for 12 h at room temperature. The reaction mixture was then quenched by the addition of saturated aqueous Na2SO4 (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phase was dried (Na2SO4) and evaporated, then the crude residue was purified by column chromatography (Rf = 0.43; n-hexane/EtOAc = 1:1).

**Synthesis of (1R,2R,3R,5R)-2-Aminomethyl-5-Isopropylbicyclo[3.1.0]Hexane-2,3-Diol Hydrochloride (7).** A solution of 6 (1.20 g, 4.20 mmol) in EtO (30 mL) was stirred with 30 mL of 5% aqueous HCl at room temperature. After 24 h, the two phases were separated, the aqueous phase was washed with EtO (3 × 30 mL) and then evaporated to dryness. Crystals formed were thoroughly washed with EtO.
Compound 7: 0.72 g (77%); colorless crystals; mp: 146–148 °C; $\alpha^2_D^{10}$ = +42 (c = 0.250; MeOH). $^1$H NMR (500 MHz, D$_2$O) $\delta$ (ppm): 0.41 (1H, dd, $J$ = 3.9, 5.6 Hz), 0.54–0.59 (1H, m), 0.85 (3H, d, $J$ = 6.9 Hz), 0.97 (3H, d, $J$ = 6.8 Hz), 1.30 (1H, dd, $J$ = 3.6, 8.5 Hz), 1.47 (1H, septet, $J$ = 6.8 Hz), 1.75 (1H, dd, $J$ = 10.0, 11.7 Hz), 2.15 (1H, dd, $J$ = 7.4, 12.3 Hz), 3.10 (2H, s), 3.66 (1H, dd, $J$ = 7.9, 8.7 Hz). $^{13}$C NMR (125.8 MHz, D$_2$O) $\delta$ (ppm): 11.8, 18.6, 19.1, 26.7, 31.6, 32.0, 33.2, 45.0, 72.8, 77.0. Anal. calc'd for Cl(NO$_2$)$_2$: C 54.17; H 9.09; N 6.32. Found: C 54.28; H 9.29; N 6.01.

**Synthesis of (1R,2R,3R,5R)-2-((Benzylamino)Methyl)-5-Isopropylbicyclo[3.1.0]Hexane-2,3-Diol (9).** To a solution of aminodiol 8 liberated from 7 (0.37 g, 2 mmol) in dry ethanol (20 mL) benzaldehyde (0.32 g, 3 mmol) was added in one portion, and the solution was stirred at room temperature for 1 h and then evaporated to dryness. The residual product was dissolved again in dry ethanol (20 mL) and stirred for a further 1 h. Next NaBH$_4$ (0.23 g, 6 mmol) was added in small portions to the mixture under ice cooling. After stirring for 48 h, the mixture was evaporated to dryness and the residue was dissolved in H$_2$O and extracted with CH$_2$Cl$_2$ (3 × 30 mL). The combined organic layer was dried (Na$_2$SO$_4$), filtered and evaporated to dryness. The obtained crude product was purified by column chromatography on silica gel (R$_f$ = 0.21; toluene/ethanol = 4/1).

Compound 9: 0.31 g (56%); colorless crystals; mp: 111–113 °C; $\alpha^2_D^{10}$ = +41 (c = 0.250; MeOH). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ (ppm): 0.22 (1H, dd, $J$ = 4.0, 5.3 Hz), 0.32–0.36 (1H, m), 0.87 (3H, d, $J$ = 6.9 Hz), 0.97 (3H, d, $J$ = 6.8 Hz), 1.14 (1H, dd, $J$ = 3.7, 8.5 Hz), 1.32 (1H, septet, $J$ = 6.8 Hz), 1.63 (1H, dd, $J$ = 9.8, 11.5 Hz), 2.02 (1H, dd, $J$ = 7.3, 12.3 Hz), 2.62 (1H, d, $J$ = 11.9 Hz), 2.91 (1H, d, $J$ = 11.9 Hz), 3.52 (1H, t, $J$ = 7.8 Hz), 3.79 (1H, d, $J$ = 13.2 Hz), 3.85 (1H, d, $J$ = 13.2 Hz), 7.26–7.36 (5H, m). $^{13}$C NMR (125.8 MHz, CDCl$_3$) $\delta$ (ppm): 13.1, 19.6, 19.7, 29.5, 31.7, 32.8, 34.1, 54.2, 55.0, 75.0, 77.6, 127.2, 128.2, 128.5, 139.7. Anal. calc'd for Cl(NO$_2$)$_2$: C 74.14; H 9.15; N 5.09. Found: C 74.25; H 9.10; N 5.15.

**Synthesis of (1R,2R,3R,5R)-3′-Benzyl-5-Isopropylspiro[bicyclo[3.1.0]Hexane-2,5′-Oxazolidin]-3-Ol (10).** To the solution of 9 (0.15 g, 0.54 mmol) in EtO (5 mL) 35% aqueous formaldehyde solution (2 mL) was added. The reaction mixture was stirred for 1 h at room temperature, followed by making it alkaline with 10% cold aqueous KOH solution and extracted with EtO (3 × 20 mL). The organic layers were combined, washed with saturated NaCl solution (3 × 20 mL) then dried (Na$_2$SO$_4$), filtered, and evaporated to dryness. The crude product was purified by column chromatography on silica gel (R$_f$ = 0.64; toluene/ethanol = 4/1).

Compound 10: 0.14 g (90%); pale-yellow oil; $\alpha^2_D^{10}$ = +63 (c = 0.250; MeOH). $^1$H NMR (500 MHz, CD$_2$Cl$_2$) $\delta$ (ppm): 0.27–0.32 (2H, m), 0.84 (3H, d, $J$ = 6.8 Hz), 0.93 (3H, d, $J$ = 6.8 Hz), 1.17–1.21 (1H, m), 1.24–1.32 (1H, m), 1.56 (1H, dd, $J$ = 10.1, 11.2 Hz), 1.78 (1H, dd, $J$ = 7.1, 11.7 Hz), 2.68 (1H, d, $J$ = 11.0 Hz), 2.93 (1H, d, $J$ = 11.0 Hz), 3.41 (1H, dd, $J$ = 9.4, 16.8 Hz), 3.75 (2H, s), 4.13 (1H, d, $J$ = 4.5 Hz), 4.25 (1H, d, $J$ = 9.5 Hz), 4.41 (1H, d, $J$ = 4.4 Hz), 7.22–7.37 (5H, m). $^{13}$C NMR (125.8 MHz, CD$_2$Cl$_2$) $\delta$ (ppm): 13.5, 20.2, 20.2, 30.5, 31.9, 32.9, 34.2, 57.9, 58.0, 74.2, 86.7, 87.3, 127.4, 128.7, 129.0, 139.8. Anal. calc'd for Cl(NO$_2$)$_2$: C 75.22; H 8.77; N 4.87. Found: C 75.31; H 8.91; N 4.70.

**Synthesis of (1R,3S,4S,5S)-4-Hydroxymethyl-1-Isopropylbicyclo[3.1.0]Hexan-3-Ol (11).** Method A: to a cooled (0 °C) solution of sabinoil 1 (0.15 g, 1 mmol) in 3 mL dry THF under nitrogen atmosphere, a solution of 1 M borane THF complex (2 mL) was injected dropwise. After completing the addition, the mixture was allowed to warm to room temperature and stirred for 2.5 h. After completion of hydroboration 0.5 mL of cold water was added and the mixture was stirred for 10 min. This was followed by adding 0.3 mL of 3 N aqueous solution of NaOH and then 0.3 mL of 35% H$_2$O$_2$. The mixture was stirred for an additional 30 min, then quenched by the addition of 5 mL ice-cold water and extracted with EtOAc (3 × 10 mL). The organic phases were collected, washed with brine, dried over Na$_2$SO$_4$ and evaporated. The residue was subjected to chromatography on silica gel (R$_f$ = 0.21; n-hexane/EtOAc = 3/2).


Method B: to a cooled (0 °C) solution of sabinol 1 (0.15 g, 1 mmol/L) in 5 mL dry THF under argon atmosphere 0.21 mL of 95% solution of borane dimethyl sulfide complex (BMS) in DMS was injected, then the reaction mixture was allowed to warm up to room temperature and stirred for 18 hours. The work up of the reaction mixture was the same as for Method A.

Compound 11: Method A: 0.08 g, (47%); Method B: 0.12 g (70%); colorless crystals; mp: 66–68 °C; \([\alpha]_{D}^{20} = +35 \quad (c = 0.250; \text{MeOH})\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) (ppm): 0.31–0.35 (1H, m), 0.85–0.89 (4H, m), 0.93 (3H, d, \(J = 6.8\) Hz), 0.95–0.99 (1H, m), 1.37 (1H, septet, \(J = 6.8\) Hz), 1.75 (1H, d, \(J = 14.1\) Hz), 2.08 (1H, ddd, \(J = 1.4, 6.8, 14.2\) Hz), 2.10 (1H, s), 2.46–2.53 (1H, m), 3.83 (1H, dd, \(J = 9.0, 10.6\) Hz), 3.90 (1H, dd, \(J = 5.5, 10.7\) Hz), 4.41 (1H, t, \(J = 6.5\) Hz). \(^13\)C NMR (125.8 MHz, CDCl\(_3\)) \(\delta\) (ppm): 13.9, 19.8, 19.9, 24.2, 32.7, 33.0, 38.5, 47.7, 62.5, 73.3. Anal. calc'd for C\(_{13}\)H\(_{20}\)O: C 70.55; H 10.66. Found: C 70.48; H 10.79.

Synthesis of (1R,3S,5R)-3-Benzoxyl-1-Isopropyl-4-Methylenecyclo[3.1.0]Hexane (12). To a stirred suspension of NaH (6 mmol/L) in dry, freshly distilled THF (10 mL), a THF solution (3 mL) of 1 (0.30 g, 2 mmol/L) was added at room temperature under argon atmosphere. After 30 min stirring, a solution of benzyl bromide (0.34 g, 2 mmol) in THF (3 mL) was added dropwise at room temperature, and the reaction mixture was kept at boiling temperature for 1 h. The reaction was quenched by the addition of H\(_2\)O (2 mL), and then THF was removed under reduced pressure to about 10% of the initial volume. After adding ice-cold water (25 mL) to the obtained residue, the aqueous phase was extracted with CH\(_2\)Cl\(_2\) (4 × 20 mL), then the organic phase was dried (NaSO\(_4\)), filtered and evaporated to dryness. The crude residue was purified by flash column chromatography on silica gel (R\(_f\) = 0.80; n-hexane/EtOAc = 19:1).

Compound 12: 0.45 g (92%); pale-yellow oil; \([\alpha]_{D}^{20} = +7 \quad (c = 0.250; \text{MeOH})\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) (ppm): 0.69–0.73 (1H, m), 0.87 (3H, d, \(J = 6.9\) Hz), 0.93 (3H, d, \(J = 6.8\) Hz), 1.18–1.21 (1H, m), 1.46 (1H, septet, \(J = 6.8\) Hz), 1.64 (1H, ddd, \(J = 2.4, 8.5\) Hz), 1.89 (1H, d, \(J = 13.9\) Hz), 2.05 (1H, ddd, \(J = 1.4, 7.3, 13.8\) Hz), 4.08 (1H, d, \(J = 7.2\) Hz), 4.32 (1H, d, \(J = 11.8\) Hz), 4.57 (1H, d, \(J = 11.7\) Hz), 4.88 (1H, s, 5.11 (1H, s), 7.27–7.39 (5H, m). \(^13\)C NMR (125.8 MHz, CDCl\(_3\)) \(\delta\) (ppm): 18.6, 19.7, 19.8, 29.1, 32.6, 35.7, 36.7, 69.8, 81.3, 108.4, 127.3, 127.7, 128.3, 138.7, 152.3. Anal. calc'd for C\(_{13}\)H\(_{20}\)O: C 84.25; H 9.15. Found: C 84.43; H 9.33.

3.2. General Procedure for the Preparation of 13 and 14

To a solution of 1 or 12 (0.66 mmol/L) in acetone (5 mL) 4-methylmorpholine N-oxide (0.33 mL, 50% aqueous solution) and OsO\(_4\) (0.25 mL, 2% tert-BuOH solution) were added, and the reaction mixture was stirred for 24 h at room temperature. Then, the reaction was quenched by the addition of saturated aqueous Na\(_2\)SO\(_4\) (5 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was dried (NaSO\(_4\)) and evaporated. The purification of the crude product was accomplished by column chromatography on silica gel (13: R\(_f\) = 0.15, 14: R\(_f\) = 0.40; n-hexane/EtOAc = 3:2).

\((1R,2R,3S,5R)-2-Hydroxyethyl-5-isopropylbicyclo[3.1.0]hexane-2,3-diol (13): \quad 0.10 \quad \text{g} \quad (81%); \quad \text{white crystalline powder; mp:} \quad 148–150 \degree \text{C}; \quad \([\alpha]_{D}^{20} = +4 \quad (c = 0.250; \text{MeOH})\). \(^1\)H NMR (500 MHz, CD\(_3\)SO) \(\delta\) (ppm): 0.18–0.24 (1H, m), 0.82 (3H, d, \(J = 6.8\) Hz), 0.84 (1H, t, \(J = 4.1\) Hz), 0.90 (3H, d, \(J = 6.8\) Hz), 0.96–1.01 (1H, m), 1.34 (1H, septet, \(J = 6.8\) Hz), 1.46 (1H, d, \(J = 13.2\) Hz), 2.09 (1H, ddd, \(J = 1.0, 6.6, 13.0\) Hz), 3.42 (1H, dd, \(J = 6.3, 11.0\) Hz), 3.55 (1H, dd, \(J = 5.4, 11.0\) Hz), 3.69–3.73 (1H, m), 4.08 (1H, t, \(J = 5.8\) Hz), 4.12 (1H, s), 4.42 (1H, d, \(J = 4.1\) Hz). \(^13\)C NMR (125.8 MHz, CD\(_3\)SO) \(\delta\) (ppm): 12.5, 19.8, 20.0, 30.0, 31.8, 32.3, 36.1, 63.8, 76.9, 83.4. Anal. calc'd for C\(_{13}\)H\(_{20}\)O: C 64.49; H 9.74. Found: C 64.60; H 9.88.

\((1R,2R,3S,5R)-3-Benzoxyl-2-hydroxyethyl-5-isopropylbicyclo[3.1.0]hexan-2-ol (14): \quad 0.08 \quad \text{g} \quad (44%); \quad \text{colorless semi-solid;} \quad \([\alpha]_{D}^{20} = +4 \quad (c = 0.250; \text{MeOH})\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) (ppm): 0.41–0.46 (1H, m), 0.90 (3H, d, \(J = 6.9\) Hz), 0.94–0.97 (1H, m), 0.98 (3H, d, \(J = 6.8\) Hz), 1.04–1.08 (1H, m), 1.44 (1H, septet, \(J = 6.8\) Hz), 1.88 (1H, d, \(J = 13.9\) Hz), 2.11 (1H, ddd, \(J = 1.6, 6.6, 13.9\) Hz), 3.66 (1H, d, \(J = 11.4\) Hz), 3.73 (1H, d, \(J = 6.5\) Hz), 3.94 (1H, d, \(J = 11.4\) Hz), 4.27 (1H, d, \(J = 11.8\) Hz), 4.57 (1H, d, \(J = 11.8\) Hz), 7.26–
3.3. General Procedure for the Preparation of 17 and 18

Method A: to a mixture of 1 (1.00 g, 6.57 mmol) dissolved in 50 mL CHCl₃ and NaHPO₄·12H₂O (3.40 g, 9.49 mmol) dissolved in 100 mL water (pH = 9.2), m-chloroperbenzoic acid (75% purity, 7.47 mmol) was added in one portion at 0 °C, and the mixture was stirred at room temperature. When the reaction was complete, as indicated by TLC (1 h), the mixture was separated, and the aqueous phase was extracted with CHCl₃ (100 mL). The organic layer was washed with 10% NaOH solution (3 × 50 mL), dried (Na₂SO₄), and evaporated. The residue was purified by column chromatography on silica gel to afford a mixture of 17 and 18 (0.78 g, 37%, 17:18 = 2:1). Product 17 (0.30 g) was isolated in pure form by recrystallization from CHCl₃/n-hexane.

Method B: to a solution of 1 (0.50 g, 3.28 mmol) in 25 mL CHCl₃ and NaHPO₄·12H₂O (1.70 g, 4.74 mmol) in 50 mL water (pH = 9.2), a solution of m-chloroperbenzoic acid (75% purity, 3.74 mmol) in CHCl₃ (25 mL) was added dropwise over 10 min at 0 °C, and the mixture was stirred at room temperature. When the reaction was complete, as indicated by TLC (1 h), the mixture was separated, and the aqueous phase was extracted with CHCl₃ (50 mL). The organic layer was washed with saturated aqueous solution of NaHCO₃ (3 × 50 mL), dried (Na₂SO₄), and evaporated to afford 18 as the single product.

((1R,2S,3R,4S,5R)-2,3-Dihydroxy-5-isopropylbicyclo[3.1.0]hexan-2-yl)methyl 3-chlorobenzoate (17). Method A, 0.30 g (14%, in isolated pure form); white crystals; mp: 93–96 °C; [α]D²⁰ = +22 (c = 0.250; MeOH). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 0.48–0.52 (1H, m), 0.87 (3H, d, J = 6.9 Hz), 0.92 (3H, d, J = 6.8 Hz), 1.16 (1H, t, J = 4.2 Hz), 1.30–1.37 (2H, m), 1.89 (1H, d, J = 14.3 Hz), 2.10 (1H, ddd, J = 1.1, 7.0, 14.2 Hz), 2.54 (1H, br s), 2.81 (1H, br s), 3.95 (1H, d, J = 7.0 Hz), 4.30 (1H, d, J = 11.6 Hz), 4.39 (1H, d, J = 11.6 Hz), 7.40 (1H, d, J = 7.9 Hz), 7.55 (1H, d, J = 8.0 Hz), 7.96 (1H, d, J = 7.9 Hz), 8.04 (1H, s). ¹³C NMR (125.8 MHz, CDCl₃) δ (ppm): 13.7, 19.5, 19.7, 29.5, 32.4, 32.8, 35.2, 69.4, 72.9, 80.7, 127.9, 129.8, 131.5, 133.3, 134.7, 165.6. Anal. calcd for C₁₇H₂₁ClO₄: C 62.86; H 6.52. Found: C 63.01; H 6.60.

((1R,3S,4S,5R)-4-Hydroxy-4-hydroxymethyl-1-isopropylbicyclo[3.1.0]hexan-3-yl) 3-chlorobenzoate (18). Method B, 0.40 g (38%); white crystalline powder; mp: 110–112 °C; [α]D²⁰ = +12 (c = 0.250; MeOH). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 0.55–0.61 (1H, m), 0.91 (3H, d, J = 6.9 Hz), 0.95 (3H, d, J = 6.8 Hz), 1.23 (1H, t, J = 4.4 Hz), 1.38 (1H, septet, J = 6.8 Hz), 1.75 (1H, dd, J = 3.7, 8.6 Hz), 1.87 (1H, d, J = 14.1 Hz), 2.16 (1H, ddd, J = 1.5, 7.2, 14.2 Hz), 2.19 (1H, br s), 3.03 (1H, br s), 3.83 (1H, d, J = 12.6 Hz), 3.96 (1H, d, J = 12.6 Hz), 4.37 (1H, d, J = 7.0 Hz), 7.40 (1H, t, J = 7.9 Hz), 7.55 (1H, d, J = 8.0 Hz), 7.91 (1H, d, J = 7.8 Hz), 8.00 (1H, s). ¹³C NMR (125.8 MHz, CDCl₃) δ (ppm): 15.1, 19.9, 20.0, 27.7, 32.9, 33.2, 35.2, 66.9, 73.7, 94.0, 128.3, 130.2, 132.6, 133.8, 134.3, 135.1, 166.8. Anal. calcd for C₁₇H₂₁ClO₄: C 62.86; H 6.52. Found: C 62.97; H 6.75.

Synthesis of (1R,2S,3S,5R)-2-Hydroxymethyl-5-isopropylbicyclo[3.1.0]hexane-2,3-Diol (19). To a solution of 17 or 18 (33 mg, 0.10 mmol) in EtOH (2 mL), a 10% cold aqueous solution of NaOH (1 mL) was added at room temperature. The reaction mixture was stirred for 30 min, then concentrated under reduced pressure to evaporate ethanol, and the aqueous residue was extracted with CHCl₃ (3 × 3 mL). The combined organic extract was washed with brine, dried (Na₂SO₄) and evaporated.

Compound 19: 17 mg (91%); white crystalline powder; mp: 90–92 °C; [α]D¹⁰ = +45 (c = 0.250; MeOH). ¹H NMR (500 MHz, (CD₃)₂SO) δ (ppm): 0.22–0.26 (1H, m), 0.80 (3H, d, J = 6.8 Hz), 0.85 (3H, d, J = 6.8 Hz), 0.94 (1H, t, J = 3.9 Hz), 1.03 (1H, dd, J = 3.5, 8.5 Hz), 1.23 (1H, septet, J = 6.8 Hz), 1.55 (1H, d, J = 13.6 Hz), 1.89 (1H, ddd, J = 1.0, 7.1, 13.6 Hz), 3.21 (1H, dd, J = 6.4, 11.1 Hz), 3.33 (1H, ddd, J = 5.6, 11.1 Hz), 3.64–3.68 (1H, m), 3.95 (1H, s), 4.44 (1H, d, J = 3.8), 4.55 (1H, t, J = 5.9 Hz). ¹³C NMR (125.8 MHz, (CD₃)₂SO) δ (ppm): 13.2, 19.4, 19.5, 29.2, 31.2, 32.0, 35.0, 66.8, 71.1, 80.8. Anal. calcd for C₁₀H₁₅O₃: C 64.49; H 9.74. Found: C 64.69; H 9.83.
3.3. General Procedure for the Reaction of Aldehydes with Diethylzinc in the Presence of Chiral Catalyst

To the respective catalyst (0.1 mmol), 1 M EtZn in n-hexane solution (3 mL, 3 mmol) was added under an Ar atmosphere at room temperature. The reaction was stirred for 25 min at room temperature (see Table 1), and benzaldehyde (1 mmol) was then added to the solution with subsequent stirring at room temperature (see Table 1) for a further 20 h. The reaction was quenched with a saturated NH₄Cl solution (15 mL), and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic phase was washed with H₂O (10 mL), dried (Na₂SO₄), and evaporated under vacuum. The crude secondary alcohols obtained were purified by flash column chromatography (Rf = 0.54; n-hexane/EtOAc = 4/1). The ee and absolute configuration of the resulting material were determined by chiral HPLC analysis on a Chiralcel OD-H column and the data are as follows: 1-phenyl-1-propanol; V(n-hexane)/V(2-propanol) = 95: 5, 0.7 mL/min, 215 nm, tR₁ = 6.29 min for R-isomer, tR₂ = 6.73 min for S-isomer [7].

3.4. X-Ray Structure Determination of 11

Single crystals of 11 were grown by warming up 11 in heptane until almost full dissolution, and then the solution was abruptly cooled in an ice bath. X-ray intensity data were collected at −123 °C on a Rigaku UltraX 18S generator (Xenocs mirrors, Mo Kα radiation, λ = 0.71073 Å) using a MAR345 image plate. The images were interpreted and integrated with CrysalisPRO[48], and the implemented absorption correction was applied. Using Olex2 [49], the structures were solved with the ShelXS [50] structure solution program by Direct Methods, and refined with the ShelXL [51] refinement package using full-matrix least-squares minimization on F². Non-hydrogen atoms were refined anisotropically, and hydrogen atoms in the riding mode with isotropic temperature factors fixed at 1.2 times Ueq of the parent atoms (1.5 for the –CH₃ and the –OH groups). Because compound 11 is composed of only light atoms (C, H, O), it was not possible to determine its absolute configuration. CCDC number 1814013 contains the supplementary crystallographic data.

Crystal Data for C₈H₁₃O₃: (M =170.24 g/mol): orthorhombic, space group P2₁2₁2₁: (no. 19), a = 6.1474(2) Å, b = 8.1525(3) Å, c = 19.6783(6) Å, V = 986.21(6) Å³, Z = 4, T = 150.15 K, μ(MoKα) = 0.078 mm⁻¹, Dcalc = 1.147 g/cm³, 8206 reflections measured (10.216° ≤ 2θ ≤ 52.006°), 1915 unique (Rint = 0.0310, Rsigma = 0.0189) which were used in all calculations. The final R₁ = 0.0328 (I > 2σ(I)) and wR₂ was 0.0848 (all data).

4. Conclusions

In conclusion, we have developed a library of new chiral sabinol-based aminodiol, diol, and triol derivatives (6–19). Our results revealed that functionalization of (+)-sabinol occurred with high stereoselectivity, affording only a single diastereomeric product in each case. Stereoselectivities, however, were found to be lower as compared with other monoterpenic-based trifunctional catalysts. It is surmised that, because of the appreciable steric influence of the bicyclic ring system and the freely rotating hydroxymethyl or aminomethyl group, a stable transition state could not be formed in the reactions of the applied catalysts and EtZn. From this point of view, aminodiolhs have proven to be more efficient catalysts compared to diol or triol derivatives.

On the other hand, because of the observed different reactivity of the functional groups (caused by the steric hindrance of the bicyclic system of sabinane skeleton), the obtained aminodiol, diols, and triols may serve as useful building blocks for the synthesis of new heterocyclic ring systems and biologically active compounds.

**Supplementary Materials:** The following are available online at www.mdpi.com/links, ¹H, ¹³C NMR, HSQC, HMBC, COSY, and NOESY spectra of new compounds (S3–S24) and crystal structure of diol 11 (S25).

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**Author Contributions:** The listed authors contributed to this work as described in the following. Zsolt Szakonyi, Wim Dehaen and Yerlan M. Suleimen designed, planned research, interpreted the results. Yerbolat Tashenov and
Mathias Daniels planned research, interpreted the results and carried out of the synthetic work. Koen Robeyns and Luc Van Meervelt performed X-ray experiments. All authors discussed the results, prepared and commented on the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds 3–17 are available from the authors.

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