CHEMISTRY
A European Journal

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Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201802484

Link to VoR: http://dx.doi.org/10.1002/chem.201802484

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FULL PAPER

Regio- and stereoselective synthesis of bicyclic limonene-based chiral aminodiols and spirooxazolidines

Tam Minh Le[a], Antal Csámpai[b], Ferenc Fülöp [a,c], Zsolt Szakonyi*[a,d]

Abstract: A library of monoterpene-based aminodiols was synthesized and applied as chiral catalysts in the addition of diethylzinc to benzaldehyde. The reduction of a bicyclic *α*-methylene ketone, derived from natural (-)-limonene followed by epoxidation, gave the key intermediate epoxy alcohol. Ring opening of the oxirane ring with primary amines induced by lithium perchlorate afforded the required aminodiols. The substituent-dependent ring closures of secondary aminodiols with formaldehyde resulted in both spirooxazolidines and a fused 1,3-oxazine. Cyclisation reactions of the studied aminodiols, resulting in spirocyclic oxazolidines and an isomeric perhydro-1,3-oxazine-fused compound along with the possible iminium intermediates, were analyzed by a systematic series of comparative DFT modelling carried out at B3LYP/6-31+G(d,p) level of theory.

Introduction

Chiral synthons that can be applied successfully in asymmetric homogenous and heterogeneous catalysis are of increasing importance in organic chemistry.[1–3] A large number of natural products such as *α*- and *β*-pinene,[4–6] 2- and 3-carene[7,8] and (+)-pulegole[9,10] serve as important starting materials for the synthesis of bi- and trifunctional chiral compounds and heterocycles. Monoterpene-based 1,2- and 1,3-amino alcohols have been demonstrated to be excellent chiral auxiliaries in a wide range of stereoselective transformations including intramolecular radical cyclisations,[11] intramolecular [2+2] photocycloaddition[12] and Grinard addition.[13,14]

Furthermore, aminodiols, combining the chemical properties of 1,2- and 1,3-amino alcohols derived from naturally occurring terpenes, are excellent starting materials and catalysts of stereoselective synthesis.[15–20] Moreover, aminodiols are excellent building blocks for the synthesis of 1,3-oxazines and oxazolidines. Depending upon the hydroxy group involved in ring closure with the amino group, five- to six-membered rings may be formed stereoselectively. The resulting bicyclic heterocycles bearing a free hydroxy group can contribute to high enantioselective inductions in asymmetric addition reactions.[21–24]

Besides their chemical interest, some natural aminodiols exhibit marked biological activity. For example, aristeromycin, first isolated from *Streptomyces citricolor* and its modified derivatives belong to an important group of carbocyclic nucleosides that exhibit a wide range of pharmacological properties such as antiviral, anticancer and antitoxoplasma activities. Aristeromycin analogues, in particular, are widely used as antiviral agents against a range of viruses, including human immunodeficiency, hepatitis B, herpes simplex, varicella-zoster, influenza and hepatitis C virus.[25–27] Other aminodiols may serve as starting materials for the synthesis of biologically active natural compounds. For example, cytoxazone a microbial metabolite isolated from *Streptomyces* species is a selective modulator of secretion of T_H2 cytokine.[26,27]

In the present contribution we report the stereoselective synthesis of new bicyclic 3-amino-1,2-diols as potential building blocks and chiral auxiliaries starting from commercially available natural (-)-limonene. In addition, we have studied the substituent-dependent ring closure of these aminodiols with formaldehyde. Competitive ring closure processes can provide both spirooxazolidine ring systems and condensed 1,3-oxazines. The results of experimental and theoretical study of these synthons may expand our knowledge of this type of trifunctional building blocks in the design/construction of 3D small molecules.

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10.1002/chem.201802484

Results and Discussion

Chiral bicyclic aminodiols were prepared from commercially available (-)-limonene **1** starting with regioselective hydroxylation to afford allylic alcohol **2**.[28–30] The resulting allylic alcohol was oxidized to aldehyde **3**,[28] which was then converted to carboxylic acid **4** applying a literature method.[31–34] Intramolecular acylation of isoperillic acid **4** performed using earlier methods[34,35] resulted in bicyclic methylene ketone **5** as a single product (Figure 1).

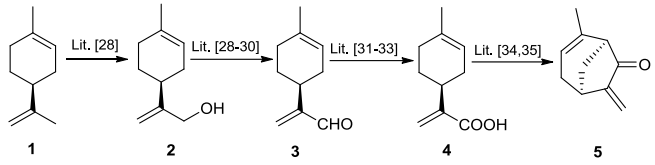
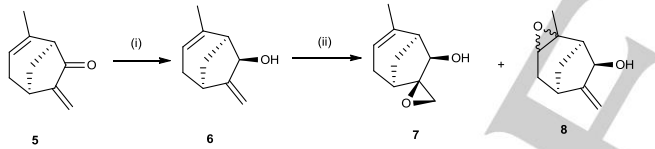


Figure 1. Synthesis of bicyclic methylene ketone **5**

Stereoselective reduction of **5** gave allylic alcohol **6** according to a literature procedure applied for similar monoterpenic β-methylene ketones.[10] Epoxidation of **6** in dry toluene in the presence of vanadyl acetylacetonate as catalyst gave a mixture of **7** and **8**. Note that **8** exists as a 4:1 mixture of two diastereomers (Scheme 1).[36–38] In addition, it is interesting that the ratio of **7** and **8** depends on the temperature.



Scheme 1. (i) $NaBH_4$, MeOH, 0 °C, 4 h, 67%; (ii) 70% *t*-BuOOH, $VO(acac)_2$, dry toluene, 25 °C, 12 h, 60% (optimised combined yield of **7** and **8**).

While at 25 °C **7** was formed as the main product, the ratio of the two products was found to be 1:1 at 100 °C. At lower temperature, the yield dropped dramatically despite the elongated reaction time without any significant change in the **7** to **8** ratio (Table 1). The yield of **7** could not be increased by either changing the ratio of **6** and the oxidation reagent or the temperature (Table 1).

The separation of epoxide **7** and **8** could not be effectively performed without decomposition of the products.

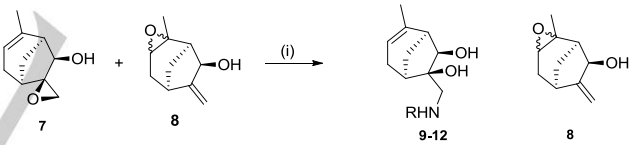
Since our earlier results clearly demonstrated that substituents at nitrogen of aminodiols definitely influenced the efficiency of their catalytic activity,[4,39] aminodiol library **9**-**12** was prepared by aminolysis of epoxide **7** with primary amines and lithium perchlorate as catalyst (Scheme 2).[7,17,39,40]

Table 1. Epoxidation reaction of **6**

Entry	**6** (mol)	*t*-BuOOH (mol)	T [°C]	t [h]	Ratio [**7**:**8**] [a]	Yield [%][b]
1	1	1.5	0	> 96	4:1	40
2	1	1.5	25	12	3:1	60
3	1	1.5	100	4	1:1	70
4	1	3.0	0	48	1:1	60
5	1	3.0	25	6	1:1	65

[a] Based on ^{1}H-NMR measurements of the crude product. [b] Isolated, combined yield of **7** and **8**.

When *tert*-butylamine was applied, the opening of the oxirane ring failed, which clearly shows that from the point of view of steric hindrance, the isopropyl group represents the upper limit of the *N*-substituent. Accordingly, our efforts in the opening of epoxide with secondary amines was also unsuccessful.[41] Interestingly, during aminolysis with primary amines under the applied conditions, epoxide **7** was transformed preferentially while **8** did not react. This is probably due to steric hindrance exerted by the methyl group of **8** at the α position. Therefore, aminodiols **9**-**12** could be easily separated from **8** on a gram scale by simple column chromatography with good yields.



9: R = CH_2Ph; **10**: R = CH(Me)Ph (*S*); **11**: R = CH(Me)Ph (*R*); **12**: R = $CH(Me)_2$

Scheme 2. (i) RNH_2, $LiClO_4$, MeCN, 70-80 °C, 4 h, 50-67%

The relative configurations of compounds **9-12** were determined by means of NOESY experiments: clear NOE signals were observed between the H-1 and H-9, H-9 and H-6, H-6 and H-5, H-8 as well as OH-6 and OH-7 protons (Figure 2). Debenzylation via hydrogenolysis of compounds **9**-**11** over Pd/C in MeOH resulted in primary aminodiol **13** in moderate yield (Scheme 3).

Since the ring closure of monoterpene-based aminodiols with rigid structures enhances their catalytic potential,[7,8] we incorporated one of the hydroxy groups of compounds **9**-**12** into a condensed 1,3-oxazine or spirooxazolidine ring.[42–44] When aminodiols **9**-**11** were reacted with formaldehyde at room temperature, spirooxazolidines **14-16** were obtained in a highly regioselective ring closure. In contrast,

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aminodiol **12** yielded a mixture of spirooxazolidine **17** and 1,3-oxazine **18**.[45]

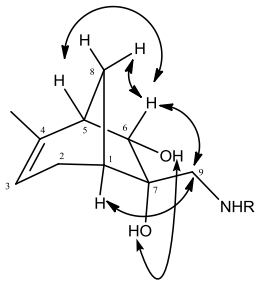
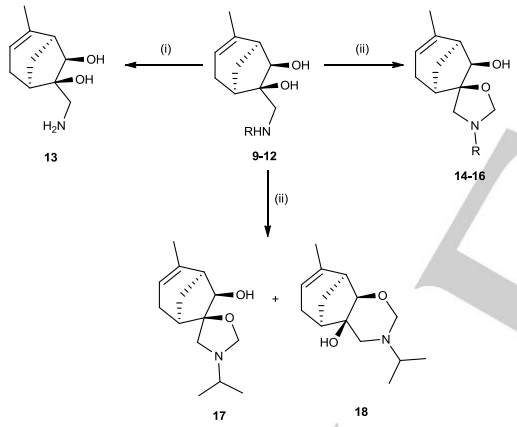


Figure 2. Determination of the aminodiol structures by NOESY

The temperature strongly affected the ratio of the two products. At low temperature (0 °C), exclusive formation of compound **17** was observed, while **17** and **18** were formed in a ratio of 2:1 at 25 °C. At higher temperature, no significant changes in the **17**/**18** ratio could be achieved (Scheme 3). Applying *p*-toluenesulfonic acid (TsOH) as additive to decrease the pH to 1-2, the ratio of **17** and **18** did not change significantly (**17**:**18** = 1.7:1) and, at the same time, the product yield dropped to 40%.



Scheme 3. from **9**-**11**, 5% Pd/C, MeOH, H_2, 1 atm, 25 °C, 20 h, 70%, (ii) R = 35% HCHO sol., Et_2O, 0 °C, 1 h, 60-70%

In order to get insight into the experienced substrate dependence of the acid-catalyzed, formaldehyde-mediated cyclisation reactions of the studied aminodiols, all resulting spirocyclic oxazolidines and isomeric perhydro-1,3-oxazine-fused compound **18** along with the possible iminium intermediates (Schemes 4 and 5) were analyzed by a systematic series of comparative DFT modelling carried out at B3LYP/6-31+G(d,p) level of theory.[46,47]

Each optimized structure, representing global or local minimum on the potential energy surfaces, features a characteristic intramolecular hydrogen-bond network involving the skeletal OH groups. Of note that in the optimized structures of iminium intermediate types **22-24** the proximal C=C double bond in the seven-membered ring is also involved in these systematically assembled H-bonding networks as a π-donor component.

The calculated relative energetics of the optimized structures of spirocyclic products and their oxazine-fused counterparts [ΔE(**spiro**→**oxazine**, **spiro***→**oxazine***)=11.8-13.8 kcal/mol: Schemes 4 and 5] are obviously in line with the experimental findings disclosing highly preferential formation of the spirocyclic isomers. Moreover, according to Boltzmann equation, the aforementioned large differences would principally allow the formation of fused oxazines in hardly detectable traces. However, under the acidic conditions employed for cyclisation, the relative stability of relevant pairs of iminium intermediates **22/I-24/I** and **22/II-24/II** with slightly different relative stability (0.2-1.9 kcal/mol), preformed for alternative modes of ring closure, might also be of crucial importance. It must be emphasized that even these small values are also in correlation with the preferred formation of the spirocyclic products. Nevertheless, they allow the formation of fused oxazines in experimentally detectable concentrations. On the other hand, the amount of iminium cations relative to the appropriate neutral spirooxazolidine or 1,3-oxazine components in the reaction mixtures is highly dependent on the acidity of the reaction mixture. This was spectacularly indicated by the dramatic differences (even with opposite signs) in the calculated relative energetics characterizing two selected types of reversible cyclisation reactions **14-17**+H_3O^+↔**22**$^+$**-25**$^+$+H_2O and **14-17**+$H_9O_4^+$↔**22**$^+$**-25**$^+$+4H_2O [+(52.0-80.7) kcal/mol and –(2.2-30.9) kcal/mol, respectively: Schemes 4 and 5]. Consequently, it can be assumed that under appropriate acidic conditions the aforementioned relative population of iminium cations **22**$^+$**-24**$^+$**/I**, **22**$^+$**-24**$^+$**/II**, **25**$^+$**/I**, **25**$^+$**/II**, and **25**$^+$**/III** might indirectly control the detectable relative amounts of the spirocyclic oxazolidines and fused 1,3-oxazines. Note that their interconversion under neutral conditions is prevented or significantly slowed down by high activation barriers (24.7-42.7 kcal/mol: Schemes 4 and 5).

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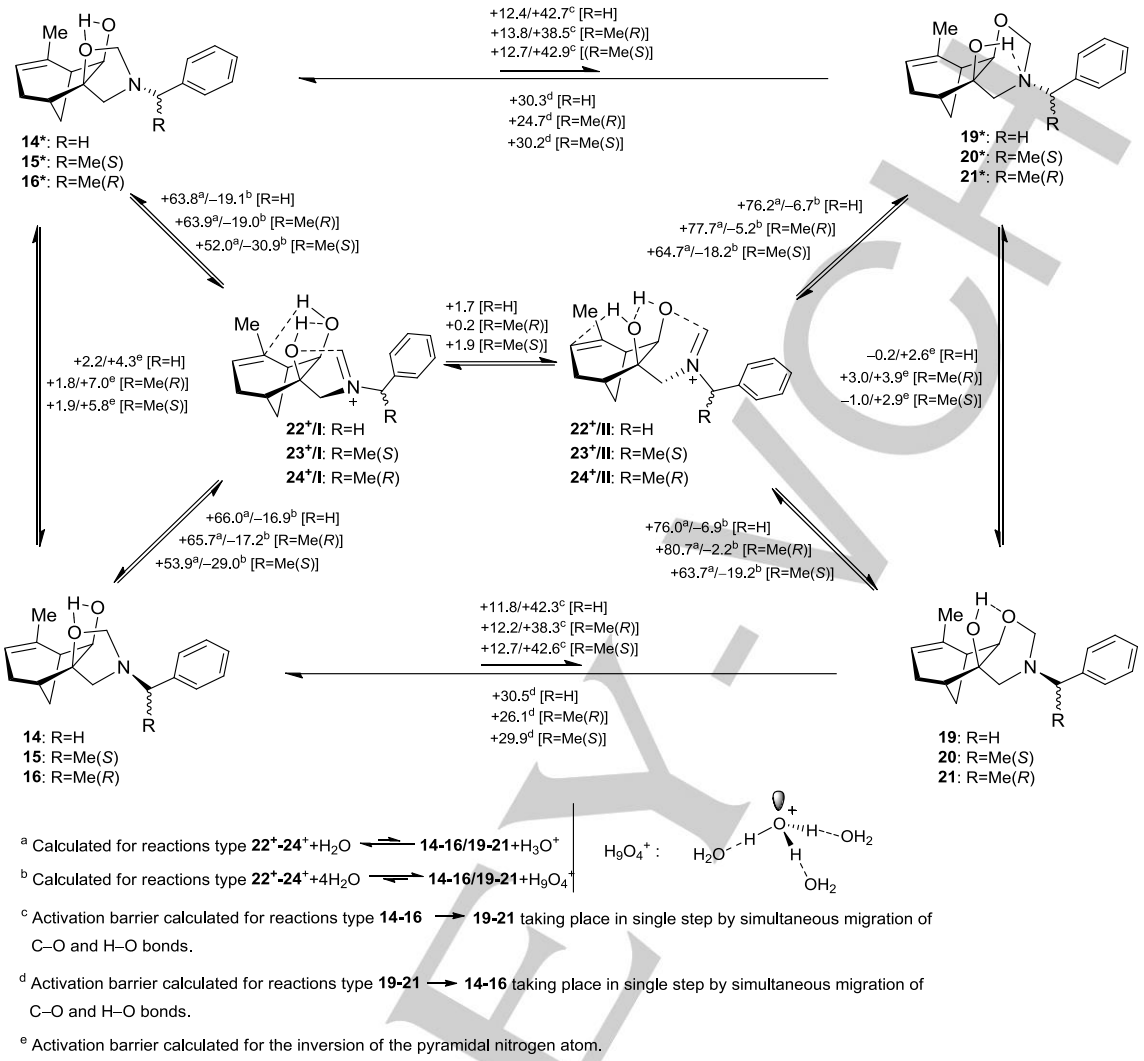

Scheme 4. Pathways, energetics and activation barriers (kcal/mol) calculated for the interconversion of **14-16, 19-21** and the relevant iminium cationic intermediates involving the inversions of the nitrogen stereogenic centre present in the neutral molecules.

The slightly enhanced tendency of isopropyl-substituted model **12** to afford fused oxazine product **18** might be due to acid-catalyzed formation of iminium cation **25$^+$/II**, the unique intermediate that is preformed to alternative modes of cyclisation, in concentration comparable to those of its rotamers **25$^+$/I** and **25$^+$/III** preformed to single modes of ring closure (Scheme 5). The assumed modes of ring closure of iminium cations are in accord with the partial bonding interactions involving the appropriate hydroxy groups and the carbenium centre as disclosed by the analysis of their bonding MO's (Figure 3). Partial C---O interactions involving the tertiary hydroxy group were disclosed in cations **22$^+$/I** and **25$^+$/I** (cf. HOMO-5 and HOMO-9, respectively), while similar interactions between the cationic centre and the secondary hydroxy group are represented by HOMO-14 and HOMO-10 in cations **22$^+$/II** and **25$^+$/III**, respectively. On the other hand, it is of pronounced interest that in cation **25$^+$/II** a three-centred interaction of the carbenium centre with both hydroxy groups spectacularly visualized by HOMO-15 gives plausible support to the view about the abovementioned alternative directions of cyclisation of this intermediate.

All calculations were carried out by using Gaussian 09 program packege.[48] Upon request, the optimized structures are provided by the authors.

Transition states were localized on the potential energy surfaces by QST2 method[49] at B3LYP level of theory using 6-31+G(d,p) basis set.

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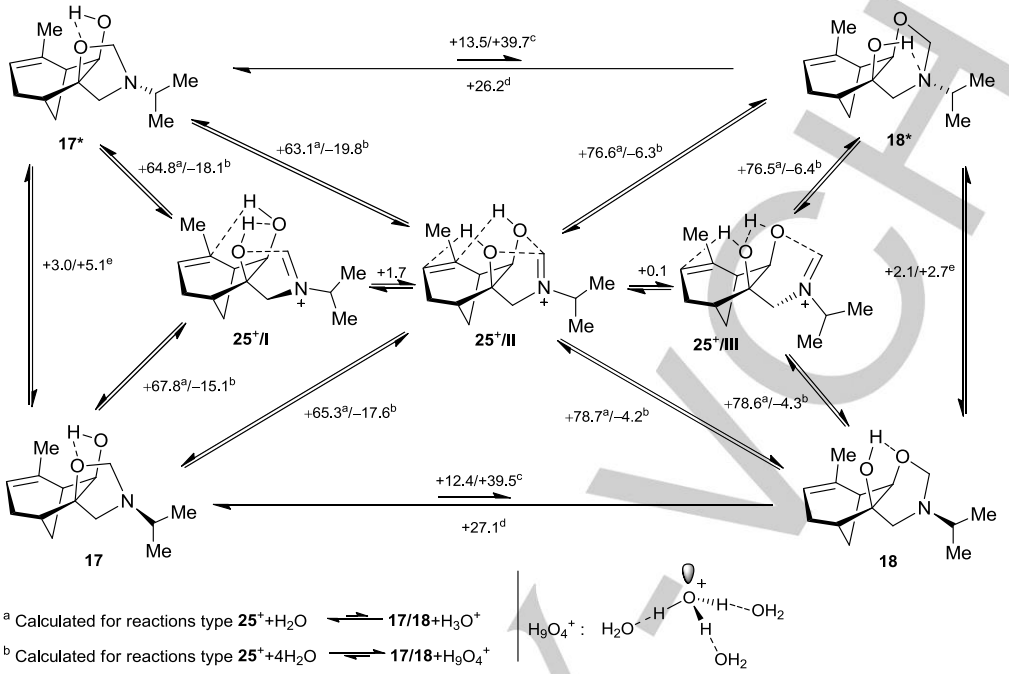
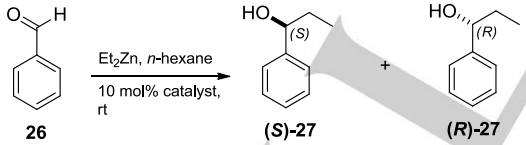


Scheme 5. Pathways, energetics and activation barriers (kcal/mol) calculated for the interconversion of **17**,**18** and the relevant iminium cationic intermediates involving the inversions of the nitrogen stereogenic centre present in the neutral molecules.

The aminodiol derivatives (**9-18**) were applied as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde (**26**) to form (*S*)- and (*R*)-1-phenyl-1-propanol **27** (Scheme 6).



Scheme 6. Model reaction for enantioselective catalysis.

The results are presented in Table 2. The enantiomeric purity of 1-phenyl-1-propanols (*S*)-**27** and (*R*)-**27** was determined by GC on a CHIRASIL-DEX CB column using literature methods.[7,8,50,51] Low to good enantioselectives were observed. Aminodiol **12** afforded the best *ee* value (*ee* = 55%) with an (*R*)-selectivity (entry 4), while a 2:1 mixture of **17**/**18** showed the best *ee* value (*ee* = 80%) with an (*S*)-selectivity (entry 10). The results obtained clearly show that the spirooxazolidine ring has poorer catalytic performance compared with the 1,3-oxazine ring system. These results are in good correlation with those observed with pinane- or sabinane-based spirooxazolidines and carane-fused 1,3-oxazines in our earlier studies.[44,52,53]

Table 2. Addition of diethylzinc to benzaldehyde, catalyzed by aminodiols, oxazolidines and 1,3-oxazines

Entry	Ligand[a]	Yield[b] (%)	*ee*[c] (%)	Configuration[d]
1	**9**	80	16	(*R*)
2	**10**	85	24	(*R*)
3	**11**	87	40	(*R*)
4	**12**	89	55	(*R*)
5	**13**	87	35	(*R*)
6	**14**	85	30	(*R*)
7	**15**	88	6	(*R*)
8	**16**	83	0	-
9	**17**	90	6	(*R*)
10	**17/18** (2:1)	87	80	(*S*)

[a] 10 mol%. [b] After silica column chromatography. [c] Determined on the crude product by GC (Chirasil-DEX CB column). [d] Determined by comparing the t_R of GC analysis and optical rotations with the literature date.

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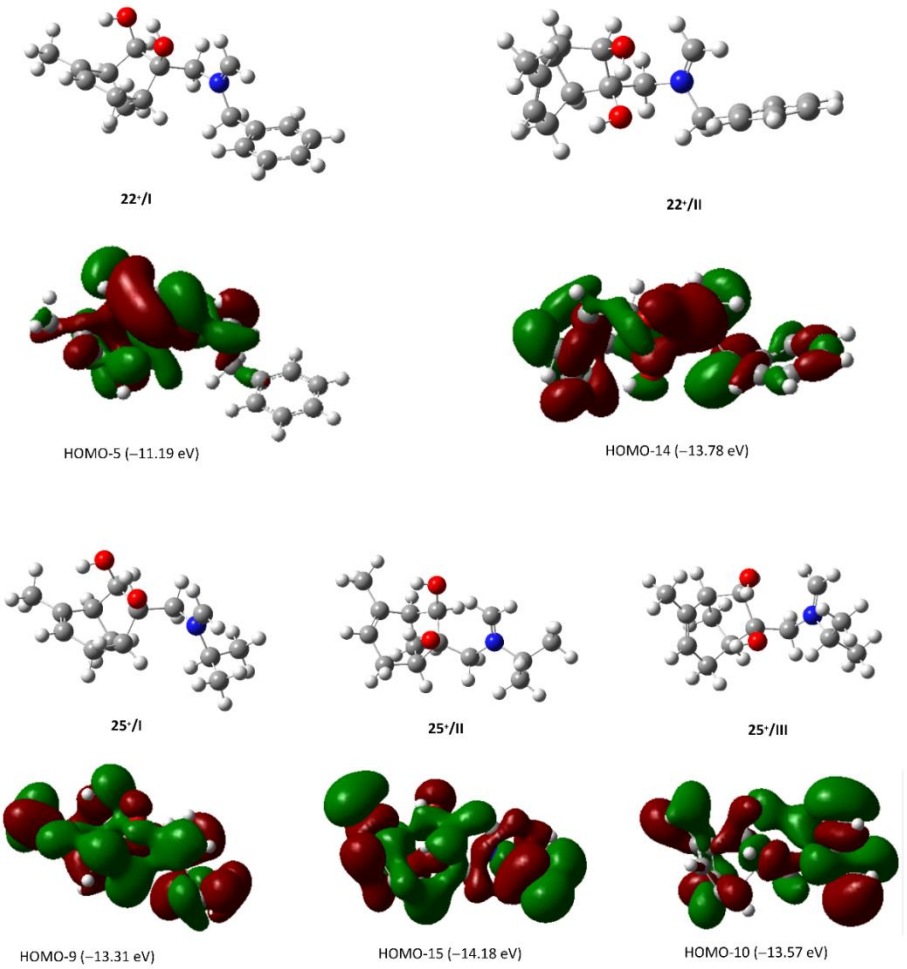

Figure 3. Selected MO's of the iminium intermediates that highlight the alternative modes of partial bonding between the nucleophilic tertiary or secondary carbinol unit and the electrophilic carbenium centre (in 22^+/I, 22^+/II, 25^+/I and 25^+/III) and the latter's simultaneous three-centred interaction with both hydroxy groups (in 25^+/II)

Conclusions

Starting from natural (-)-limonene, a limonene-based aminodiol library was created whereas the reaction of aminodiols with formaldehyde resulted in bicyclic monoterpene-fused spirooxazolidines in *N*-substituent dependent ring closures. The regioselective nature of the ring closure proved to be *N*-substituent-dependent, and molecular modelling was applied to explain this phenomenone. The aminodiols and their ring-closed derivatives were applied as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde. The 1,3-oxazine obtained proved to be a good catalyst in the addition of diethylzinc to benzaldehyde.

Experimental Section

General Methods: ^{1}H- and ^{13}C- NMR spectra were recorded on a Bruker Avance DRX 400 [400 and 100 MHz, respectively, δ = 0 ppm (TMS)] and Bruker Avance DRX 500 [500 and 125 MHz, respectively, δ = 0 ppm (TMS)]. Chemical shifts (δ) are expressed in ppm relative to TMS as internal reference. *J* values are given in Hz. Microanalyses were performed on a Perkin–Elmer 2400 elemental analyser. GC measurements were made on Perkin-Elmer Autosystem KL GC consisting of a Flame Ionisation Detector and a Turbochrom Workstation data system (Perkin-Elmer Corpotation Norwalk, USA). The separation of *O*-acetyl

derivatives of enantiomers was carried out on a CHIRASIL-DEX CB column (2500 × 0.265 mm I.D).

Optical rotations were determined with a Perkin–Elmer 341 polarimeter. Melting points were determined on a Kofler apparatus and are uncorrected. Chromatographic 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).

Starting materials: (*S*)-Limonene **1** is available commercially from Merck Co. All chemicals and solvents were used as supplied. THF and toluene were dried over Na wire. **(***S*)-Isoperillyl alcohol (**2**), (*S*)-*p*-mentha-1,8-dien-9-al (**3)**, (*S*)-*p*-mentha-1,8-dien-9-oic acid (**4**) and (1*S*,5*S*)-4-methyl-7-methylenebicyclo[3.2.1]oct-3-en-6-one (**5**) were prepared according to literature procedures, and all spectroscopic data were similar as described therein.[28],[34]

*(1S,5S,6R)-4-Methyl-7-methylenebicyclo[3.2.1]oct-3-en-6-ol (**6**):* A suspension of $NaBH_4$ (1.5 g, 39.65 mmol) in MeOH (21 mL) was added dropwise to an ice-cooled solution of **5** (1.5 g, 10.12 mmol) in MeOH (18 mL). Stirring was continued for 4 h at 0 °C. When the reaction was complete, the mixture was poured into brine and the product was extracted with diethyl ether (3 × 100 mL). The combined extracts were washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo and the crude product was used for the next step without further purification.

Compound **6**: 1.02 g (67%); white crystals; mp: 50-53 °C; $[\alpha]^{D}_{20}$ = -188 (c 0.20, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.64-1.70 (m, 3H), 1.76 (s, 3H), 1.93 (d, *J* = 16.8 Hz, 1H), 2.39-2.47 (m, 2H), 2.80 (s, 1H), 4.58 (s, 1H), 5.14 (s, 1H), 5.19 (s, 1H), 5.32 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 25.0 (CH_3), 30.6 (CH_2), 38.5 (CH_2), 38.9 (CH), 44.4 (CH), 81.3 (CH), 108.6 (CH_2), 120.1 (CH), 137.7 (C_q), 160.0 (C_q). Anal. Calcd for $C_{10}H_{14}O$: C,79.96; H, 9.39. Found: C, 79.93, H, 9.40.

*(1S,2'R,5S,7R)-2-Methylspiro[bicyclo[3.2.1]oct[2]ene-6,2'-oxiran]-7-ol (**7**) and (1R,6R,8R)-2-methyl-7-methylene-3-oxatricyclo[4.2.1.02,4]nonan-8-ol (**8**):* To a stirred pale red solution of **6** (1.0 g, 6.56 mmol) and vanadyl acetylacetonate (7 mg) in dry toluene (30 mL), briefly (Na_2CO_3) dried *t*-BuOOH (70% solution in H_2O, 1.30 g, 10.1 mmol) in dry toluene (30 mL) was added dropwise at 25 °C. The red colour of the solution darkened during the addition then faded to brownish yellow. Stirring was continued (20 h), whereupon potassium hydroxide (0.55 g, 9.8 mmol) in brine (25 mL) was added. The mixture was extracted with toluene (3 × 100 mL) and the organic layer was washed with brine before drying (Na_2SO_4) and evaporation. Flash column chromatography (*n*-hexane:ethyl acetate 4:1) gave the mixture of epoxides **7** and **8** as a pale yellow oil.

Mixture of compound **7** and **8**: 0.66 g (60%); colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.36-1.42 (5H, m, minor), 1.51-1.54 (m, minor, 1H), 1.70-1.77 (m, 5H, minor overlapped with major), 2.11-2.18 (m, 5H, minor overlapped with major), 2.42-2.44 (m, 1H, minor overlapped with major), 2.61 (br s, 1H, minor), 2.81 (d, *J* = 5.2 Hz, 1H, major), 2.92 (d, *J* = 2.6 Hz, 1H, minor), 2.96 (d, *J* = 5.2 Hz, 1H, major), 3.16 (d, *J* = 11.9 Hz, 1H, minor), 4.12-4.16 (m, 1H, major), 4.29-4.34 (m, 1H, minor), 4.95 (d, *J* = 2.2 Hz, 1H, minor), 5.10 (s, 1H, minor), 5.33 (d, *J* = 1.3 Hz, 1H, major). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 24.4 (CH_3, minor), 24.7 (CH_3, major), 28.8 (CH_2, major), 30.0 (CH_2, major), 35.3 (CH, major), 36.6 (CH_2, minor), 36.7 (CH, minor), 42.7 (CH, minor), 44.1 (CH, major), 51.6 (CH_2, major), 56.8 (CH, minor), 64.8 (C_q, major), 75.9 (CH, major), 77.4 (CH, minor), 106.3 (CH_2, minor), 119.7 (CH, major), 137.3 (C_q, major), 157.4 (C_q, minor). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.30; H, 8.50.

Isolated compound **8**: 0.16 g (15%); colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.26-1.30 (m, 3H, minor), 1.36-1.42 (m, 5H, major), 1.50-1.55 (m, 1H, major), 1.70-1.80 (m, 2H, minor), 1.96-1.98 (m, 1H, minor), 2.10-2.18 (m, 3H, minor overlapped with major), 2.41-2.43 (m, 1H, minor overlapped with major), 2.61 (br s, 1H, major), 2.86 (d, *J* = 3.5 Hz, 1H, minor), 2.92 (d, *J* = 2.5 Hz, 1H, major), 3.16 (d, *J* = 11.9 Hz, 1H, major), 3.55 (d, *J* = 12.5 Hz, 1H, minor), 4.17-4.25 (m, 1H, minor), 4.29-4.34 (m, 1H, major), 4.95 (d, *J* = 2.1 Hz, 1H, major), 5.10 (s, 1H, major). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 24.6 (CH_3, major), 30.2 (CH_2, major), 36.8 (CH_2, major), 36.9 (CH, major), 42.9 (CH, major), 57.0 (CH, major), 77.6 (CH, major), 106.5 (CH_2, major). (Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.30; H, 8.50.

General methods for epoxide ring opening with primary amines: To a solution of the mixture of epoxide **7** and **8** (0.66 g, 3.97 mmol) in MeCN (50 mL) was added a solution of the appropriate amine (7.94 mmol) in MeCN (15 mL) and $LiClO_4$ (0.07 g, 0.66 mmol). The mixture was kept at reflux temperature for 4 hours. When the reaction was completed (indicated by TLC), the mixture was evaporated to dryness, and the residue was dissolved in water (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was dried (Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography on silica gel with an appropriate solvent mixture

($CHCl_3$:MeOH 19:1). The crude products after purification were recrystallized in diethyl ether resulting in compounds **9**-**12**.

(1S,5S,6R,7R)-6-((Benzylamino)methyl)-2-methylbicyclo[3.2.1]oct-2-ene-6,7-diol (***9***): 0.54 g (50%); white crystals; mp: 190-200 °C; $[\alpha]^{D}_{20}$ = -62 (c 0.24, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm):1.45 (m, 2H), 1.61 (s, 3H), 1.97 (d, *J* = 17.2 Hz, 1H), 2.17-2.24 (m, 3H), 2.73 (d, *J* = 12.5 Hz, 1H), 2.81 (d, *J* = 12.5 Hz, 1H), 3.84 (t, *J* = 5.5 Hz, 1H), 4.01 (br s, 1H), 4.12 (s, 2H), 5.11 (s, 1H), 5.65 (d, *J* = 5.5 Hz, 1H), 7.38-7.60 (m, 5H), 8.97 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 24.8 (CH_3), 27.9 (CH_2), 28.2 (CH_2), 39.9 (CH), 43.3 (CH), 50.6 (CH_2), 54.5 (CH_2), 74.8 (C_q), 76.9 (CH), 118.8 (CH), 128.5 (CH Ar), 128.8 (CH Ar), 130.4 (CH Ar), 131.8 (C_q Ar), 137.2 (C_q). Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.73; H, 8.45; N, 5.08.

(1S,5S,6R,7R)-2-Methyl-6-((((S)-1-phenylethyl)amino)methyl)bicyclo[3.2.1]oct-2-ene-6,7-diol (***10***): 0.68 g (60%); white crystals; mp: 190-195 °C; $[\alpha]^{D}_{20}$ = -87 (c 0.21, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.39-1.43 (m, 2H), 1.60 (s, 3H), 1.65 (d, *J* = 6.7 Hz, 1H), 1.90-1.99 (m, 2H), 2.17-2.23 (m, 2H), 2.46 (d, *J* = 12.4 Hz, 1H), 2.78 (d, *J* = 12.4 Hz, 1H), 3.95 (s, 1H), 3.99 (br s, 1H), 4.31 (m, 1H), 5.10 (s, 1H), 5.67 (br s, 1H), 7.35-7.60 (m, 5H), 8.84 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 19.9 (CH_3), 24.7 (CH_3), 27.9 (CH_2), 28.1 (CH_2), 40.3 (CH), 43.4 (CH), 54.5 (CH_2), 58.4 (CH), 74.8 (C_q), 76.6 (CH), 118.7 (CH), 127.9 (CH Ar), 128.5 (CH Ar), 128.7 (CH Ar), 137.2 (C_q). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.28; H, 8.65; N, 4.89.

(1S,5S,6R,7R)-2-Methyl-6-((((R)-1-phenylethyl)amino)methyl)bicyclo[3.2.1]oct-2-ene-6,7-diol (***11***): 0.74 g (65%); white crystals; mp: 215-220 °C; $[\alpha]^{D}_{20}$ = -65 (c 0.20, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24-1.33 (m, 2H), 1.59 (s, 3H), 1.64 (d, *J* = 6.1 Hz, 3H), 1.96 (d, *J* = 18.2 Hz, 1H), 2.15-2.25 (m, 3H), 2.37 (d, *J* = 12.5 Hz, 1H), 2.81 (d, *J* = 12.3 Hz, 1H), 3.68 (t, *J* = 5.40 Hz, 1H), 3.98 (s, 1H), 4.27 (br s, 1H), 5.10 (s, 1H), 5.67 (br s, 1H), 7.36-7.63 (m, 5H), 8.97 (br s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 24.7 (CH_3), 28.0 (CH_2), 28.1 (CH_2), 43.3 (CH), 54.2 (CH_2), 58.3 (CH), 74.8 (C_q), 76.9 (CH), 118.7 (CH), 127.8 (CH Ar), 128.5 (CH Ar), 128.7 (CH Ar), 137.2 (C_q). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.30; H, 8.57; N, 4.90.

(1S,5S,6R,7R)-6-((Isopropylamino)methyl)-2-methylbicyclo[3.2.1]oct-2-ene-6,7-diol (***12***): 0.60 g (67%); white crystals; mp: 195-200 °C; $[\alpha]^{D}_{20}$ = -64 (c 0.28, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 1.24 (d, *J* = 6.2 Hz, 6H), 1.50 (d, *J* = 11.7 Hz, 1H), 1.56-1.58 (m, 1H), 1.63 (s, 3H), 2.02 (d, *J* = 16.8 Hz, 1H), 2.20-2.26 (m, 3H), 2.75 (d, *J* = 12.4 Hz, 1H), 2.93 (d, *J* = 12.5 Hz, 1H), 3.28-3.30 (m, 1H), 3.77 (t, *J* = 5.4 Hz, 1H), 4.05 (s, 1H), 5.15 (br s, 1H), 5.52 (d, *J* = 5.6 Hz, 1H), 8.01 (br s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 18.30 (CH_3), 24.8 (CH_3), 27.8 (CH_2), 28.2 (CH_2), 39.3 (CH), 43.3 (CH), 50.4 (CH), 52.3 (CH_2), 74.7 (C_q), 77.3 (CH), 119.0 (CH), 137.1 (C_q). Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.30; H, 10.25; N, 6.25.

General procedure for the ring closure of compound 9-12 with formaldehyde

Method A: To a solution of aminodiol **9**-**12** (1.8 mmol) in 5 mL diethyl ether was added 20 mL of aqueous formaldehyde (35%) and the mixture was stirred at room temperature. After 1 h, it was made alkaline with 10% aqueous KOH and extracted with diethyl ether (3 × 30 mL). After drying (Na_2SO_4) and solvent evaporation crude products **14**-**18** were purified by column chromatography ($CHCl_3$:MeOH 19:1).

Method B: To a solution of aminodiol **12** (1.8 mmol) in 5 mL diethyl ether was added 20 mL aqueous formaldehyde (30%). The mixture was stirred at 0 °C for 1 h, then it was made alkaline with 10% aqueous KOH and extracted with diethyl ether (3 × 30 mL). The organic phase was dried (Na_2SO_4) and the solvent evaporated. The crude product was purified by column chromatography ($CHCl_3$:MeOH 19:1) to afford **17**.

(1S,5S,5'R,7R)-3'-Benzyl-2-methylspiro[bicyclo[3.2.1]oct[2]ene-6,5'-oxazolidin]-7-ol (***14***)*:* Prepared by method A; 0.31 g (60%); yellow oil; $[\alpha]^{D}_{20}$ = -43 (c 0.17, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.66 (d, *J* = 11.8 Hz, 1H), 1.71 (d, *J* = 1.4 Hz, 1H), 2.06-2.11 (m, 1H), 2.21 (br s, 1H), 2.30-2.36 (m, 2H), 2.82 (d, *J* = 10.9 Hz, 1H), 3.07 (d, *J* = 10.9 Hz, 1H), 3.71-3.83 (m, 3H), 4.27 (d, *J* = 4.4 Hz, 1H), 4.55 (d, *J* = 4.4 Hz, 1H), 5.30 (s, 1H), 7.26-7.36 (m, 5H) . ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 24.9 (CH_3), 28.9 (CH_2), 29.2 (CH_2), 43.4 (CH), 44.1 (CH), 57.3 (CH_2), 65.8 (CH_2), 82.2 (CH), 85.2 (C_q), 87.9 (CH_2), 119.8 (CH), 127.5 (CH Ar), 128.6 (CH Ar), 128.9 (CH Ar), 137.4 (C_q). Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.77; H, 8.09; N, 4.95.

(1S,5S,5'R,7R)-2-Methyl-3'-((S)-1-phenylethyl)spiro[bicyclo[3.2.1]oct[2]ene-6,5'-oxazolidin]-7-ol (***15***)*:* Prepared by method A; 0.38 g (70%); yellow oil; $[\alpha]^{D}_{20}$ = -51 (c 0.28, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.33 (d, *J* = 6.5 Hz, 3H), 1.32-1.38 (m, 1H), 1.59 (d, *J* = 11.8 Hz, 1H), 1.70 (d,

J = 1.7 Hz, 3H), 2.05-2.13 (m, 2H), 2.25-2.33 (m, 2H), 2.46 (d, *J* = 9.9 Hz, 1H), 2.81 (br s, 1H), 2.87 (d, *J* = 9.9 Hz, 1H), 3.42 (q, *J* = 6.5, 13.0 Hz, 1H), 3.75 (d, *J* = 5.5 Hz, 1H), 4.13 (d, *J* = 2.9 Hz, 1H), 4.66 (d, *J* = 2.9 Hz, 1H), 5.28 (d, *J* = 1.1 Hz, 1H), 7.24-7.35 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 23.3 (CH_3), 24.9 (CH_3), 28.8 (CH_2), 29.5 (CH_2), 43.2 (CH), 44.1 (CH), 61.8 (CH), 64.2 (CH_2), 81.3 (CH), 86.3 (C_q), 86.8 (CH_2), 119.7 (CH), 127.2 (CH Ar), 127.4 (CH Ar), 128.7 (CH Ar), 137.4 (C_q), 144.9 (C_q). Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.30; H, 8.39; N, 4.70.

(1S,5S,5'R,7R)-2-Methyl-3'-((R)-1-phenylethyl)spiro[bicyclo[3.2.1]oct[2]ene-6,5'-oxazolidin]-7-ol (***16***)*:* Prepared by method A; 0.36 g (67%); yellow oil; $[\alpha]^{D}_{20}$ = -35 (c 0.26, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):1.35 (d, *J* = 6.5 Hz, 3H), 1.40-1.44 (m, 1H), 1.63 (d, *J* = 11.8 Hz, 1H), 1.70 (d, *J* = 1.8 Hz, 3H), 2.03-2.10 (m, 1H), 2.19-2.29 (m, 3H), 2.65 (d, *J* = 10 Hz, 1H), 2.79 (d, *J* = 9.0 Hz, 1H), 3.03 (d, *J* = 9.9 Hz, 1H), 3.46 (q, *J* = 6.4, 12.8 Hz, 1H), 3.80 (q, *J* = 5.7, 8.8 Hz, 1H), 4.12 (d, *J* = 3.4 Hz, 1H), 4.40 (d, *J* = 3.5 Hz, 1H), 5.26 (s, 1H), 7.24-7.34 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 23.8 (CH_3), 24.9 (CH_3), 29.0 (CH_2), 29.3 (CH_2), 43.0 (CH), 44.2 (CH), 61.4 (CH), 64.2 (CH_2), 81.9 (CH), 86.1 (C_q), 86.7 (CH_2), 119.7 (CH), 127.2 (CH Ar), 127.4 (CH Ar), 128.7 (CH Ar), 137.5 (C_q), 144.9 (C_q Ar). Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.25; H, 8.45; N, 4.65.

(1S,5S,5'R,7R)-3'-Isopropyl-2-methylspiro[bicyclo[3.2.1]oct[2]ene-6,5'-oxazolidin]-7-ol (***17***)*:* Prepared by method B; 0.34 g (70%); yellow oil; $[\alpha]^{D}_{20}$ = -47 (c, 0.15 MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.08 (dd, *J* = 7.6, 12.6 Hz, 6H), 1.42-1.48 (m, 1H), 1.66 (d, *J* = 14.7 Hz, 1H), 1.71 (d, *J* = 1.8 Hz, 3H), 2.02-2.09 (m, 1H), 2.17-2.32 (m, 3H), 2.45-2.52 (m, 1H), 2.51 (d, *J* = 11.9 Hz, 1H), 2.79 (d, *J* = 10.0 Hz, 1H), 3.10 (d, *J* = 11.7 Hz, 1H), 3.82 (dd, *J* = 7.4, 9.9 Hz, 1H), 4.06 (d, *J* = 3.3 Hz, 1H), 4.65 (d, *J* = 3.4 Hz, 1H), 5.28 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 21.8 (CH_3), 22.0 (CH_3), 24.8 (CH_3), 28.8 (CH_2), 29.4 (CH_2), 43.0 (CH), 43.9 (CH), 52.2 (CH), 63.7 (CH_2), 81.5 (CH), 86.5 (C_q), 86.7 (CH_2), 119.7 (CH), 137.2 (CH_2). Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.80; H, 9.75; N, 5.89.

(1S,5S,5'R,7R)-3'-Isopropyl-2-methylspiro[bicyclo[3.2.1]oct[2]ene-6,5'-oxazolidin]-7-ol (***17***) *and (4aR,5S,9S,9aR)-3-isopropyl-8-methyl-2,3,4,4a,5,6,9,9a-octahydro-5,9-methanocyclohepta[e][1,3]oxazin-4a-ol* (***18***)*:* Prepared by method A; 0.36 g (74%, **17**:**18** = 2:1); yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 1.24-1.28 (m, 6H, minor overlapped with major), 1.63 (s, 3H, minor overlapped with major), 1.50-1.58 (m, 2H, minor overlapped with major), 1.99-2.26 (m, 2H, minor overlapped with major), 2.18 (s, 1H, minor), 2.38 (s, 1H, major), 2.80-2.93 (m, 2H, minor), 3.27-3.30 (m, 1H, minor), 3.30 (m, 1H, major), 3.19-3.70 (m, 2H, major), 3.85 (d, *J* = 5.1 Hz, 1H, minor), 3.94 (br s, 1H, major), 4.59-4.71 (m, 2H, minor overlapped with major), 5.01 (s, 1H, major), 5.07 (s, 1H, minor), 5.14 (s, 1H, minor overlapped with major), ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 18.3 (CH_3, minor), 18.5 (CH_3, major), 24.7 (CH_3, major), 24.9 (CH_3, minor), 27.9 (CH_2, minor), 28.0 (CH_2, minor), 28.2 (CH_2, major), 28.3 (CH_2, major), 41.5 (CH, minor), 43.4 (CH, major), 50.5 (CH, minor), 52.3 (CH_2, minor), 55.2 (CH, major), 59.2 (CH_2, major), 74.7 (C_q, minor), 77.1 (CH, minor), 80.9 (CH, major), 80.9 (CH_2, minor), 82.7 (CH_2, major), 87.4 (C_q, major), 118.8 (CH, minor), 118.9 (CH, major), 136.7 (C_q, minor), 137.3 (C_q, major). Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.80; H, 9.75; N, 5.89.

General procedure for the preparation of aminodiol 13: To a suspension of palladium-on-carbon (5% Pd, 0.22 g) in MeOH (50 mL) was added aminodiols **9**-**11** (14.0 mmol) in MeOH (100 mL), and the mixture was stirred under a H_2 atmosphere (1 atm) at room temperature. When the reaction was completed (as monitored by TLC, 20 h), the mixture was filtered through a Celite pad and the solution was evaporated to dryness. The crude product was crystallized in diethyl ether, resulting in **13** as white crystals.

(1S,5S,6R,7R)-6-(Aminomethyl)-2-methylbicyclo[3.2.1]oct-2-ene-6,7-diol (***13***): 1.80 g (70%); white crystals; mp: 197-210 °C; $[\alpha]^{D}_{20}$ = -51 (c 0.20 MeOH). ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm): 1.48 (d, *J* = 11.7 Hz, 1H), 1.52-1.56 (m, 1H), 1.62 (s, 3H), 2.00 (d, *J* = 17.2 Hz, 1H), 2.15 (br s, 1H), 2.20-2.23 (m, 2H), 2.70 (d, *J* = 12.7 Hz, 1H), 2.80 (d, *J* = 12.7 Hz, 1H), 3.79 (t, *J* = 5.6 Hz, 1H), 3.97 (s, 1H), 5.14 (s, 1H), 5.53 (d, *J* = 5.7 Hz, 1H), 7.80 (br s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm): 24.8 (CH_3), 27.8 (CH_2), 28.2 (CH_2), 43.4 (CH), 47.4 (CH_2), 74.7 (C_q), 77.0 (CH), 118.9 (CH), 137.2 (C_q). Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.55; H, 9.37; N, 7.62.

General procedure for the reaction of benzaldehyde with diethylzinc in the presence of chiral catalysts: To the respective catalyst (0.1 mmol), 1 M Et_2Zn in *n*-hexane solution (3 mL, 3 mmol) was added under an argon atmosphere at room temperature. The solution was stirred for 25 min at room temperature then benzaldehyde (1 mmol) was added. After

stirring at room temperature for a further 20 h, the reaction was quenched with 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 *ee* and absolute configuration of the resulting material were determined by chiral GC on CHIRASIL-DEX CB column after *O*-acetylation in a Ac_2O/DMPA/pyridine system.

Acknowledgements

The authors are grateful for financial support from the Hungarian Research Foundation (OTKA K112442 and K115731) and for the EU-funded Hungarian grant GINOP-2.3.2-15-2016-00012.

.**Keywords**: Stereoselective synthesis • Terpenoid • Aminodiol • Molecular modelling • Oxazolidine

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10.1002/chem.201802484

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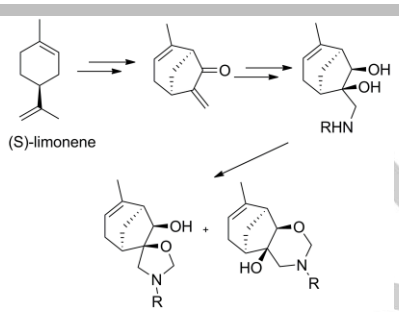
Layout 1:

FULL PAPER

Starting from natural (-)-limonene, a limonene-based aminodiol library was created whereas the reaction of aminodiols with formaldehyde resulted in limonene-fused spirooxazolidines in *N*-substituent dependent regio-selective ring closures. The aminodiol derivatives were applied as chiral catalysts in the addition of diethylzinc to benzaldehyde. The *N*-substituent-dependent ring closure was explained by comparative DFT modelling.



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Regio- and stereoselective synthesis of bicyclic limonene-based chiral aminodiols and spirooxazolidines