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**Author(s):** Bajtel, Ákos; Raji, Mounir; Haukka, Matti; Fülöp, Ferenc; Szakonyi, Zsolt

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# Stereoselective synthesis and transformation of pinane-based 2-amino-1,3-diols

Ákos Bajtel<sup>‡1</sup>, Mounir Raji<sup>‡2</sup>, Matti Haukka<sup>3</sup>, Ferenc Fülöp<sup>2,4</sup> and Zsolt Szakonyi<sup>\*2,5</sup>

## Full Research Paper

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### Address:

<sup>1</sup>Department of Pharmacognosy, University of Szeged, Eötvös u. 6, Szeged, 6720, Hungary, <sup>2</sup>Institute of Pharmaceutical Chemistry, University of Szeged, H-6720 Szeged, Eötvös u. 6, Hungary, <sup>3</sup>Department of Chemistry, University of Jyväskylä, POB 35, 40351 Jyväskylä, Finland, <sup>4</sup>Stereochemistry Research Group of the Hungarian Academy of Sciences, H-6720 Szeged, Eötvös u. 6, Hungary, and <sup>5</sup>Interdisciplinary Centre of Natural Products, University of Szeged, Szeged, Hungary

### Email:

Zsolt Szakonyi\* - szakonyi.zsolt@szte.hu

\* Corresponding author ‡ Equal contributors

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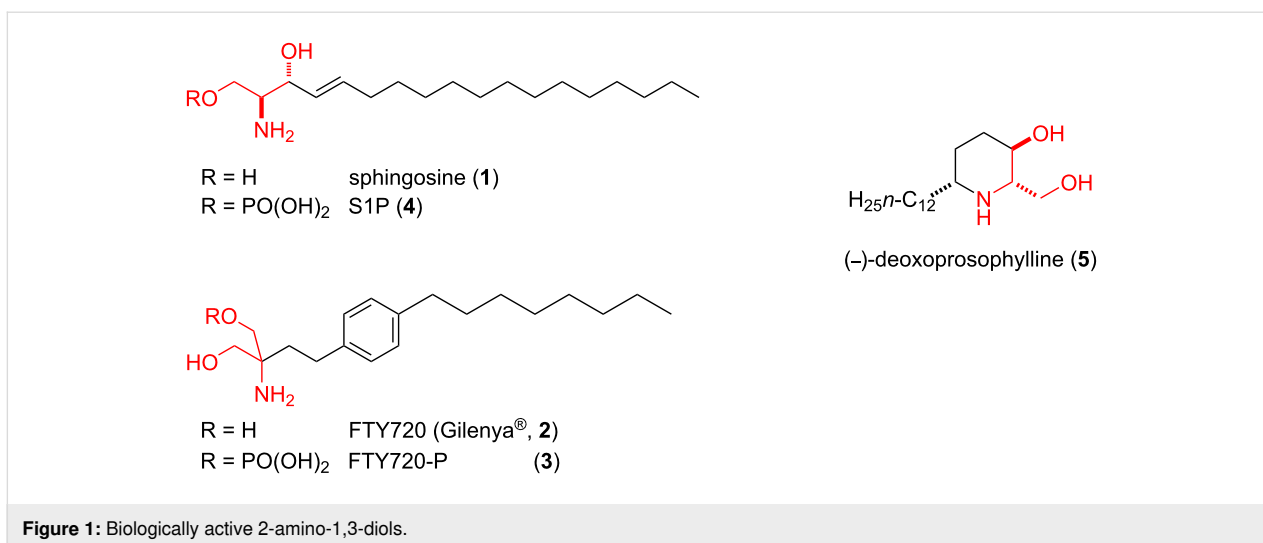
## Abstract

A library of pinane-based 2-amino-1,3-diols was synthesised in a stereoselective manner. Isopinocarveol prepared from (–)- $\alpha$ -pinene was converted into condensed oxazolidin-2-one in two steps by carbamate formation followed by a stereoselective aminohydroxylation process. The relative stereochemistry of the pinane-fused oxazolidin-2-one was determined by 2D NMR and X-ray spectroscopic techniques. The regioisomeric spiro-oxazolidin-2-one was prepared in a similar way starting from the commercially available (1*R*)-(–)-myrtenol (**10**). The reduction or alkaline hydrolysis of the oxazolidines, followed by reductive alkylation resulted in primary and secondary 2-amino-1,3-diols, which underwent a regioselective ring closure with formaldehyde or benzaldehyde delivering pinane-condensed oxazolidines. During the preparation of 2-phenyliminooxazolidine, an interesting ring–ring tautomerism was observed in CDCl<sub>3</sub>.

## Introduction

The best known 2-amino-1,3-diol derivative sphingosine (**1**) plays a crucial role in intracellular signaling as second messenger, and its derivatives called sphingolipids are also critical for cell growth, cell differentiation, cell recognition, and apoptosis [1–7]. Due to its involvement in a wide range of cellular processes, significant efforts have been made in the last two

decades targeting sphingosine analogues signalling as a therapeutic strategy. For instance, FTY720-P (**3**), the phosphate of FTY720 (**2**, fingolimod), proved to be a very good agonist for the S1P1 receptor (Figure 1). Sphingosine 1-phosphate (S1P, **4**), in turn, performed critical regulator functions in many physiological and pathological treatments, such as Alzheimer's disease



**Figure 1:** Biologically active 2-amino-1,3-diols.

[8,9], cancer [10–13], multiple sclerosis [14], and inflammation [15].

Due to the lack of a readily available natural sources and the high biological importance of sphingolipid analogues, their synthesis has been the subject of numerous studies [16]. The key step for the synthesis is the stereoselective construction of the 2-amino-1,3-diol moiety of the molecules. Generally, two main synthetic strategies are used to prepare these analogues. One requires the insertion of the alcohol and amino groups in the  $\alpha,\beta$  position with the correct stereochemistry [17–20]. The second strategy involves a bond formation between two chiral centers to produce the targeted 2-amino-1,3-diol [21,22]. For instance, deoxoprosophylline (5) as a cyclic 2-amino-1,3-diol target molecule was prepared by Kokatla et al. in an 8 step synthesis starting from Perlin aldehydes, via  $Pd(OH)_2$ -catalyzed reductive azidoketon cyclisation [23]. Another synthetic pathway involves a stereoselective aminohydroxylation process starting from allylic carbamates usually carried out in the presence of potassium osmate [24–28].

In recent years, we have extensively studied the stereoselective synthesis, as well as catalytic and pharmacological applications of monoterpene-based 3-amino-1,2-diols, which are the regioisomers of potential monoterpene 2-amino-1,3-diols [29–33]. These trifunctionalized terpenoids may also possess diverse biological activities and could successfully applied as chiral catalysts in enantioselective transformations [34]. In the present study, our aim was to synthesize novel, cyclic potentially analogues of sphingosine, incorporating a lipophilic natural pinane skeleton, starting from commercially available monoterpene-based allylic alcohols via a stereoselective hydroxyamination in the presence of a potassium osmate(VI) catalyst. We also planned to explore the regioselectivity of the ring closure of the

resulting 2-amino-1,3-diols to obtain promising 1,3-heterocycles. To reach our goal, (1*S*)-(-)- $\alpha$ -pinene (6) and (1*R*)-(-)-myrtenol (10), two naturally occurring monoterpenoids were selected as precursors, as both are commercially available, cheap starting materials.

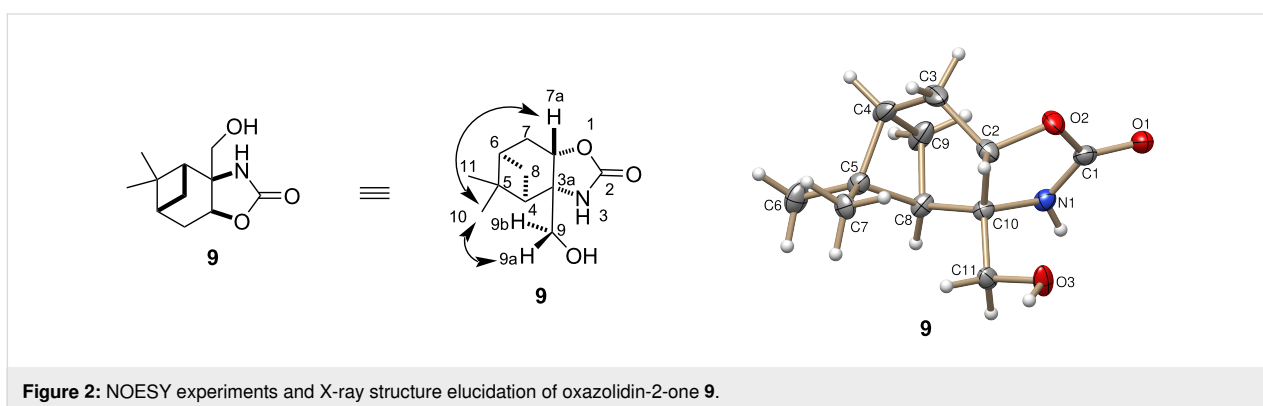
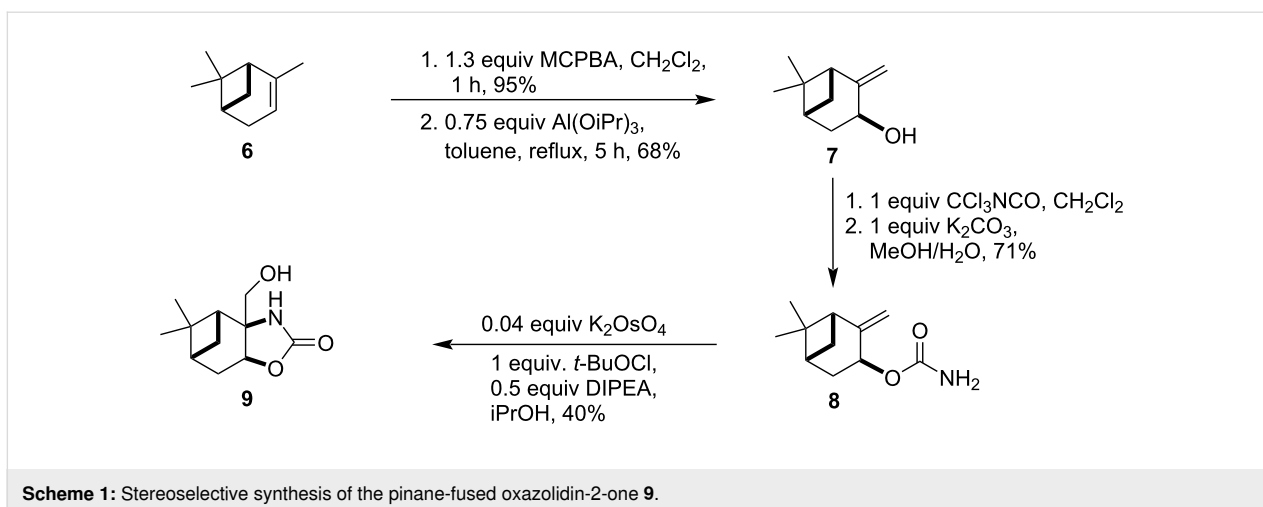
## Results and Discussion

### Synthesis of regioisomeric oxazolidinones from (1*S*)-(-)- $\alpha$ -pinene (6) and (1*R*)-myrtenol (10)

The synthesis of isopinocarveol (7), the key intermediate allylic alcohol, was performed according to a literature procedure in good yield [35]. The first step was the stereoselective epoxidation of (-)- $\alpha$ -pinene (6), carried out with *meta*-chloroperoxybenzoic acid (MCPBA), followed by a base-catalyzed allylic rearrangement mediated by aluminium isopropoxide ( $Al(OiPr)_3$ ). The resulting allylic alcohol 7 was reacted with trichloroacetyl isocyanate, followed by alkaline treatment, delivering carbamate 8 in good yield [27,28,36]. In the next step, the aminohydroxylation was accomplished by potassium osmate(VI) as the catalyst and *t*-BuOCl in the presence of DIPEA affording oxazolidine-2-one 9 [27]. The reaction was found to be highly stereoselective, giving exclusively the *diexo*-fused tricyclic 9 ring system (Scheme 1).

The absolute configuration of compound 9 was determined by 2D NMR spectroscopic techniques. Clear NOE signals were observed between the H-7a and Me-10 as well as the H<sub>a</sub>-9 and Me-10 protons. Beside NOESY experiments, the structure was also elucidated by X-ray crystallography (Figure 2).

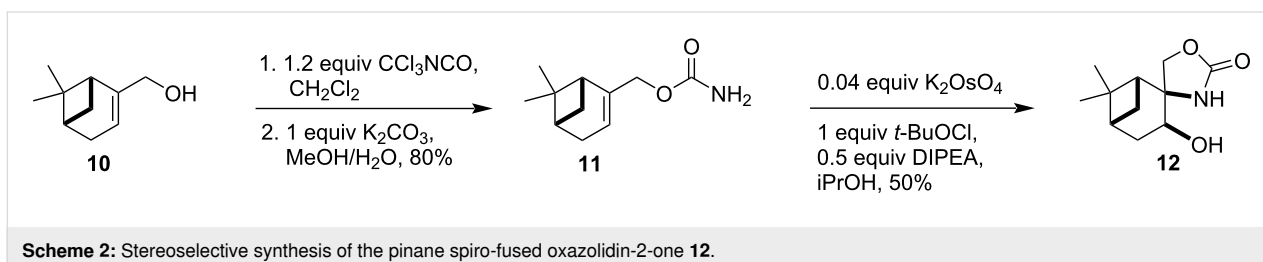
To synthesize the regioisomeric spiro-oxazolidinone derivative 12, (1*R*)-(-)-myrtenol (10) was chosen as starting material

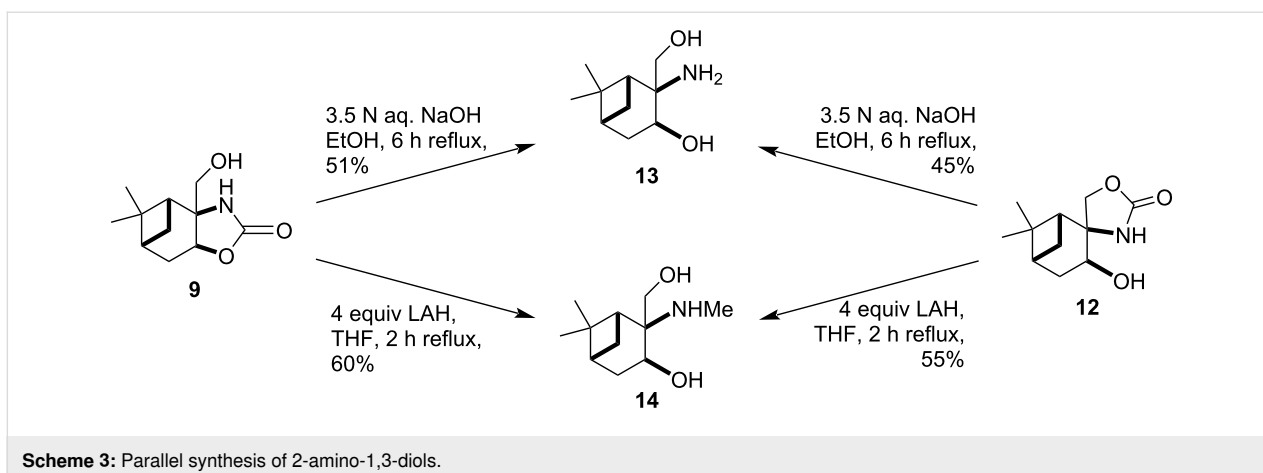


(Scheme 2). The synthetic method was similar to that mentioned above for (–)-isopinocarveol. In the first step, carbamate **11** was prepared [37], then the aminohydroxylation was carried out catalyzed by potassium osmate(VI), which led to the formation of the spiro-oxazolidine-2-one **12** in a highly regio- and stereoselective manner. Based on the NMR spectroscopic measurements of the crude product, the spiro derivative **12** was obtained exclusively with the relative configuration depicted in Scheme 2. Beside 2D NMR spectroscopic studies, the absolute configuration of compound **12** was determined by its transformation into the corresponding aminodiols **13** and **14**, comparing the products with those obtained from the regioisomer **9** (discussed in Scheme 3).

### Synthesis and transformations of pinane-based 2-amino-1,3-diols

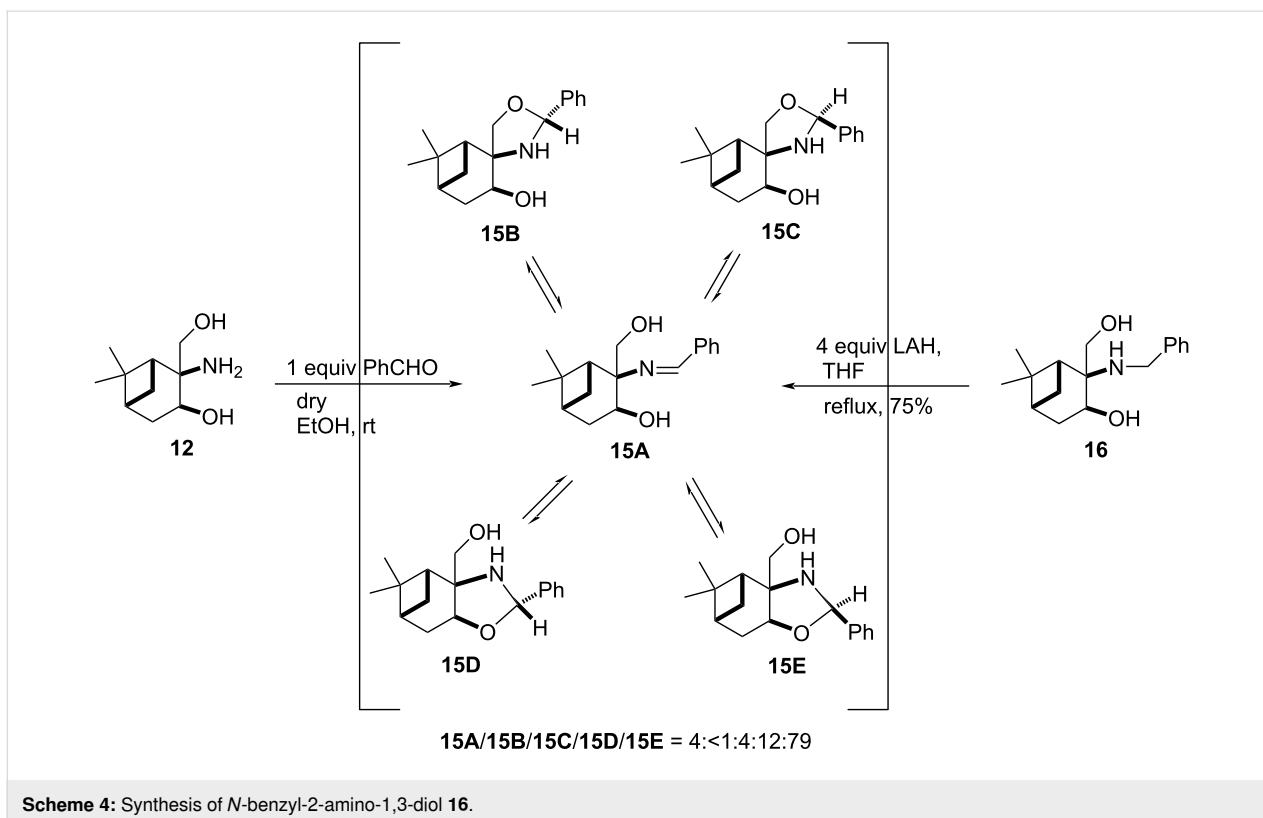
To obtain a library of pinane-based 2-amino-1,3-diols, the oxazolidin-2-ones **9** and **12** were applied as starting materials. The alkaline hydrolysis of both **9** and **12** resulted in the same primary aminodiols **13** [38]. According to the NMR spectra and other physical and chemical properties, there was no difference between the products of the two reactions. Since the relative configuration of compound **9** was clarified by NMR spectroscopy and X-ray crystallographic results, we were able to assign the stereochemistry of spiro-derivate **12**, too. In a similar manner, the  $\text{LiAlH}_4$  (LAH) reduction of both **9** and **12** gave the same *N*-methylaminodiols **14** with modest yield (Scheme 3).





Subsequently, compound **13** was reacted with benzaldehyde. In this process, the Schiff base **15A** was generated in situ. Our efforts to reduce it with sodium borohydride failed, since we did not observe the formation of the expected *N*-benzylaminodiols either at room temperature or under reflux conditions, probably due to the strong steric hindrance of the bicyclic system and the hydroxymethyl group. The  $^1\text{H}$  NMR spectroscopic measurements in  $\text{CDCl}_3$  clearly showed that the crude product was a five-component tautomeric mixture containing condensed oxazolidine **15E** as the main component. Additional minor components included the other condensed oxazolidine (**15D**),

spiro compounds **15B** and **15C** as well as the Schiff base **15A** existing in a ratio of **15A/15B/15C/15D/15E** = 4:<1:4:12:79 (Scheme 4) [39,40]. The structures of the five components **15A–E** were determined by 2D NMR spectroscopic techniques (NOESY and HMBC). Since this finding is quite unusual in the case of Schiff bases, we decided to study the ring/chain tautomeric mixture (**15A–E**) in the reaction of **13** with benzaldehyde by  $^1\text{H}$  NMR spectroscopy. When a time-dependent  $^1\text{H}$  NMR spectroscopic measurement was accomplished, we observed that the equilibrium composition was established rapidly, without any significant change in the ratio of the



tautomers. The equilibrium shifting strongly to product **15E** can account of the difficulty of the reduction process and the necessity to use a stronger reducing agent and more severe conditions. The reduction step, therefore, was performed by applying LAH, a stronger reducing agent, and longer reflux, resulting in *N*-benzyl-2-amino-1,3-diol **16** (Scheme 4).

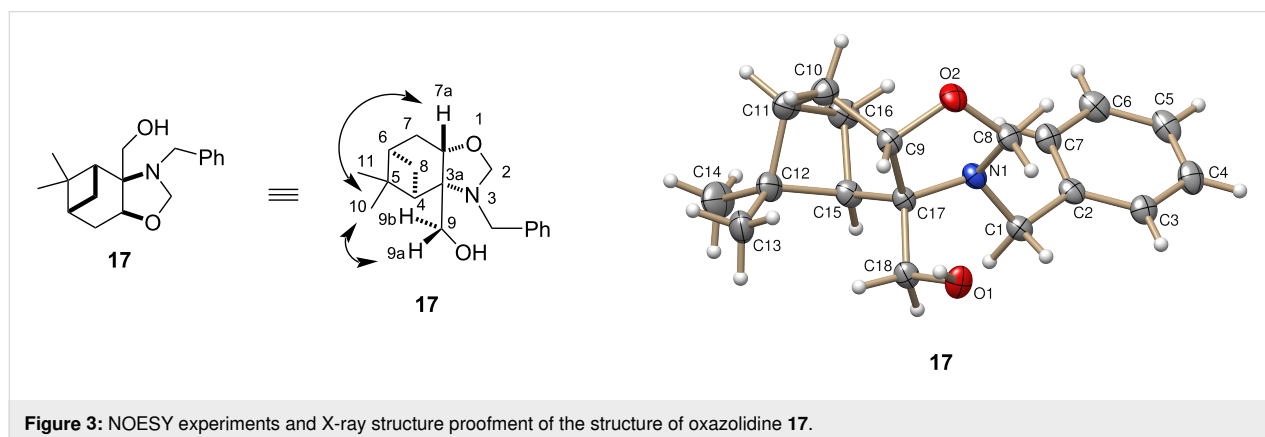
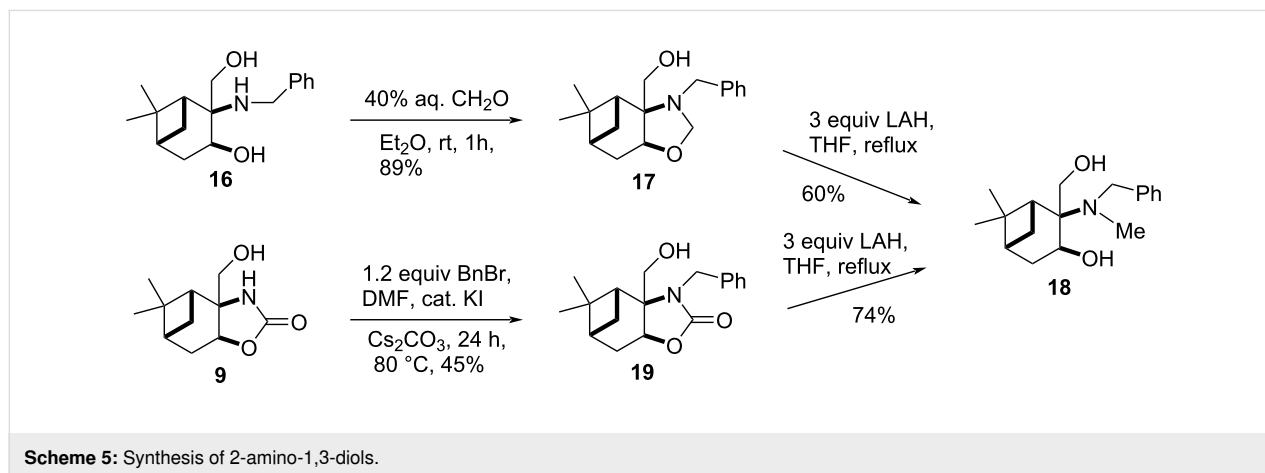
When compound **16** was treated with formaldehyde at room temperature, pinane-fused oxazolidine **17** was obtained regioselectively (Scheme 5), as it was indicated by clear HMBC correlations between the CH<sub>2</sub> of the oxazolidine ring and the annellation carbons, in contrast to the results observed in the case of the regioisomeric 3-amino-1,2-diols, where spiro-oxazolidines formed exclusively [41]. The configuration of oxazolidine **17** was determined by 2D NMR spectroscopic techniques. Clear NOE signals were observed between the H-7a and Me-10 as well as the H<sub>a</sub>-9 and Me-10 protons. In addition to NOESY experiments, the structure was also elucidated by X-ray crystallography (Figure 3).

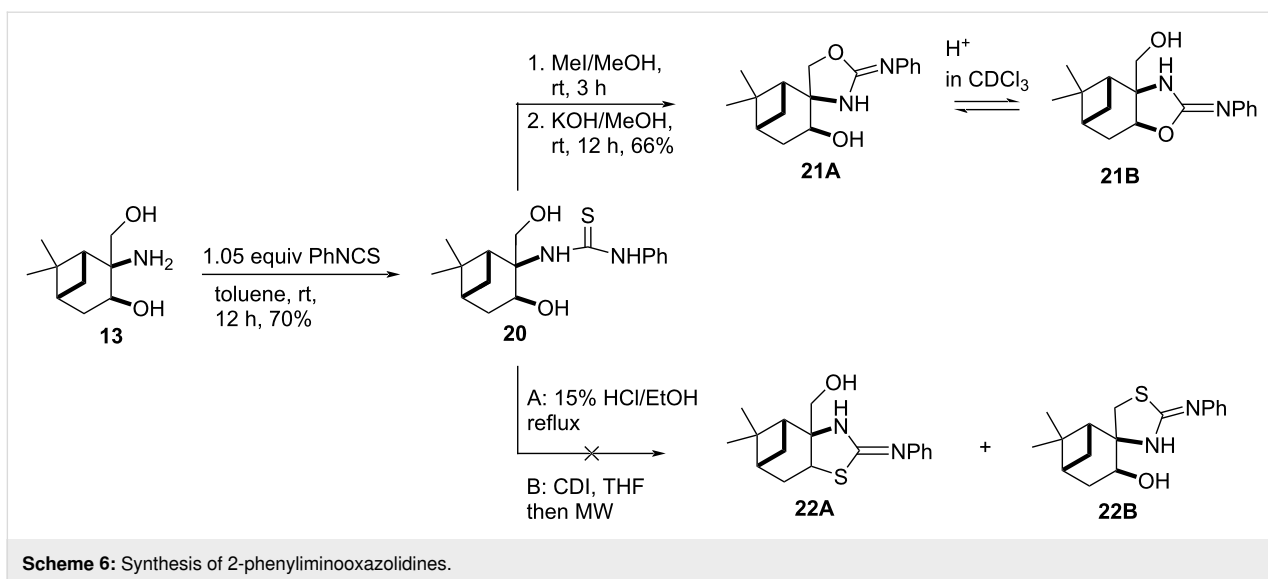
The LAH reduction of oxazolidine **17** gave *N*-benzyl-*N*-methyl analogue **18** which, alternatively, was prepared directly from

2-oxazolidinone **9** via *N*-benzylation followed by LAH reduction in 2 steps.

When compound **13** was reacted with phenylisothiocyanate, thiourea **20** was obtained, which underwent a regioselective ring closure resulting in **21A**. The structure of **21A** was determined by <sup>1</sup>H (whereas the CH-OH gave a doublet in DMSO-*d*<sub>6</sub> while the CH<sub>2</sub>-OH of **21B** could be detected as triplet) and 2D NMR spectroscopic techniques (HMBC). It is important to mention that this regioselectivity is the opposite to that observed in the reaction of aminodiols **13** and **16** with aldehydes (see Scheme 4 and Scheme 5), but it is similar to that observed in our earlier study with pinane-based 3-amino-1,2-diols [41]. During the NMR spectroscopic study of **21A** in CDCl<sub>3</sub> for 30 days, an unknown slow ring–ring tautomerization was observed, forming a 1:1 mixture of the two regioisomers **21A** and **21B**. Compound **21B** could be isolated from the mixture by column chromatography in pure form.

The synthesis of the heteroanalogue 2-phenyliminothiazolidines **22A** and **22B** failed, even when the reaction was attempted under acidic or even milder conditions (Scheme 6).





The proposed reaction pathway for the ring–ring tautomerism of **21A** and **21B** is presented in Figure 4 and it explains why the acidic environment (present generally in  $\text{CDCl}_3$  solution) is necessary. In a similar manner, an oxazolidine–1,3-oxazine tautomerism of pulegone-based 3-amino-1,2-diols was recently reported [31]. When compound **21A** or **21B** were treated in less protic solvents such as  $\text{DMSO}-d_6$  or  $\text{CD}_3\text{OD}$ , tautomerization was not observed.

## Conclusion

A small library of pinane-based 2-amino-1,3-diols was synthesized in a stereoselective manner starting from (1*R*)-(–)-myrtenol and isopinocarveol prepared from  $\alpha$ -pinene. Pinane-condensed or spiro-oxazolidin-2-ones were formed in three steps by a stereoselective hydroxyamination process. The relative stereochemistry of new compounds was determined by 2D NMR spectroscopic and X-ray techniques. The resulting primary and secondary 2-amino-1,3-diols underwent a regioselective

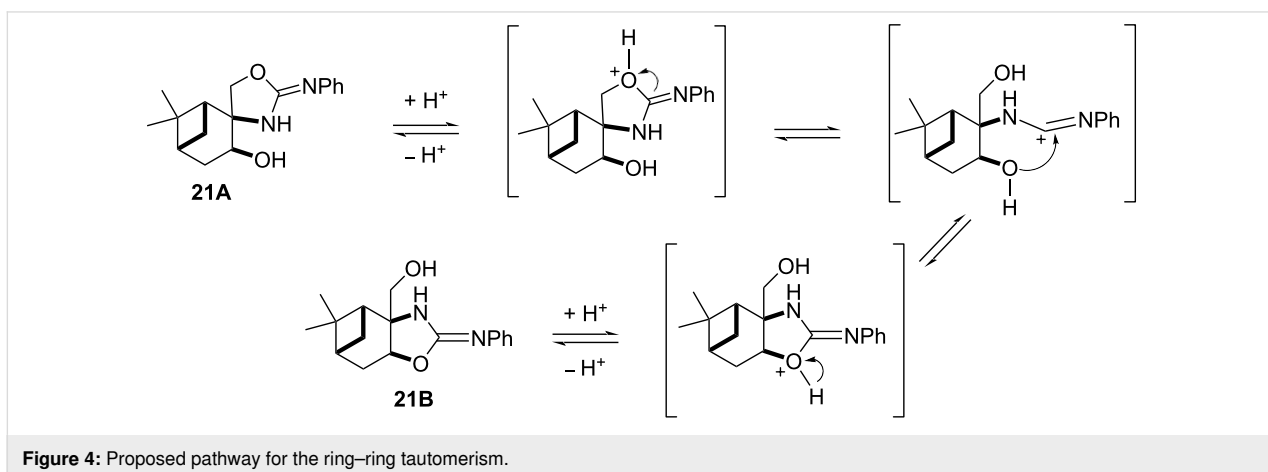
ring closure with formaldehyde and benzaldehyde producing pinane-condensed oxazolidines. In the case of 2-phenyliminooxazolidine, an interesting ring–ring tautomerism was observed in  $\text{CDCl}_3$ . The prepared trifunctional compounds may serve as chiral catalysts in enantioselective transformations, while the 2-phenyliminooxazolidines could be interesting in the field of antiproliferative or antioxidants studies based on our former studies on 2-imino-1,3-heterocycles [42,43].

## Supporting Information

### Supporting Information File 1

Experimental part, analytical data, NMR spectra and X-ray data of the prepared compounds.

[<https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-17-80-S1.pdf>]



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## ORCID® iDs

Ákos Bajtel - <https://orcid.org/0000-0003-2128-6522>  
 Mounir Raji - <https://orcid.org/0000-0002-2661-1286>  
 Matti Haukka - <https://orcid.org/0000-0002-6744-7208>  
 Ferenc Fülöp - <https://orcid.org/0000-0003-1066-5287>  
 Zsolt Szakonyi - <https://orcid.org/0000-0003-2432-8409>

## Preprint

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