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Synthesis and transformation of sphingosine analogue pinane-based 2-amino-1,3-diols

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Abstract

A library of pinane-based 2-amino-1,3-diols, analogues of biologically active sphingosine, was synthesised in a stereoselective manner. Isopinocarveol prepared from (–)-α-pinene was converted to 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 technics. The regioisomeric spiro-oxazolidin-2-one was prepared in a similar way starting from commercially available (1*R*)-(–)-myrtenol (**8**). Reduction or

alkaline hydrolysis of oxazolidines followed by reductive alkylation resulted in primary and secondary 2-amino-1,3-diols, which underwent 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 $CDCl_3$.

Keywords

monoterpene; sphingosine; oxazolidin-2-one; aminodiol; stereoselective, tautomerism

Introduction

Sphingosine (**1**), a 2-amino-1,3-diol derivative, plays a crucial role in intracellular signalling 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 analogue 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 receptor S1P1. Sphingosine 1-phosphate (S1P, **4**), in turn, performed critical regulator function in many physiological and pathological treatments, such as Alzheimer disease [8,9], cancer [10–13], multiple sclerosis [14] and inflammation [15]. Furthermore, according to the results of Naz and Arish, it is also a potentially good candidate against the COVID-19 virus [16].

Due to the lack of a readily available natural source and the high biological importance of sphingolipid analogues, their synthesis has been the subject of several studies [17]. As literature indicates, the key step for the synthesis of these sphingosine analogues regardless of their structural diversity 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 α,β position according to the correct stereochemistry [18–21]. The second strategy involves bond formation between two chiral centres to produce the targeted 2-amino-1,3-diol [22,23]. For instance, Michael addition followed by intramolecular cyclisation of alkynone and the γ-amino alcohol moiety followed by diastereoselective hydrogenation can afford a cyclic 2-amino-1,3-diol such as Deoxoprosophylline (**5**). Another synthetic pathway involves the stereoselective aminohydroxylation process starting from allylic carbamates carried out usually in the presence of potassium osmate [24–28].

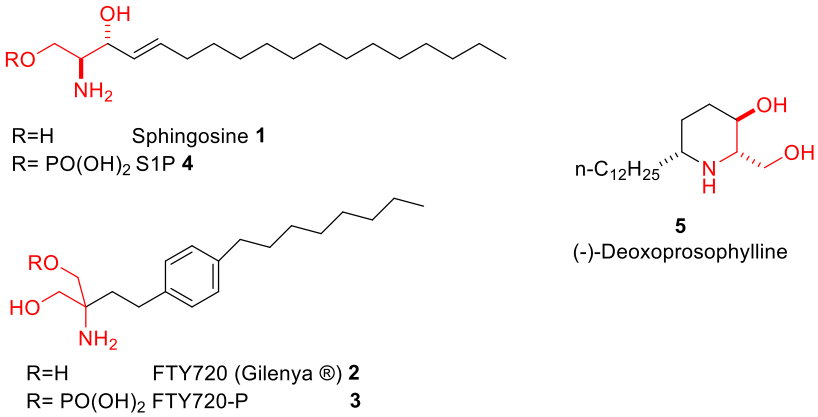


Figure 1: Biologically active 2-amino-1,3-diols.

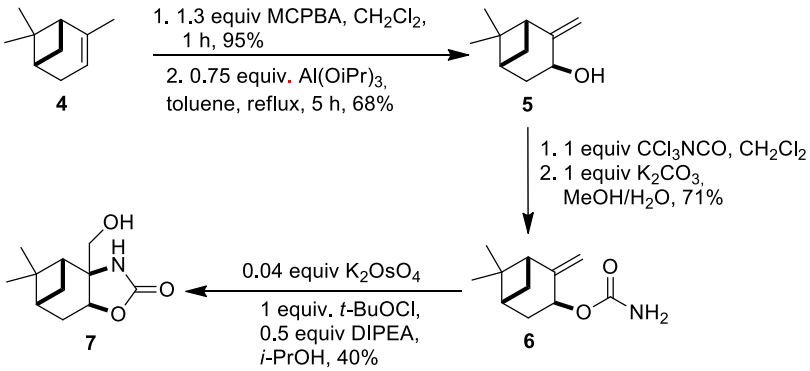
In recent years, we have extensively studied the stereoselective synthesis as well as catalytic and pharmacological applications of monoterpene-based 3-amino-1,2-diols, which are the regioisomers of potential monoterpenic 2-amino-1,3-diols [29–33]. In the present study, our aim was to synthesise novel, cyclic sphingosine analogues, incorporating a lipophilic natural pinane skeleton, starting from commercially available monoterpene-based allylic alcohols via stereoselective hydroxyamination in the presence of a potassium osmate(VI) catalyst. We also plan 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*)-(–)-α-pinene (**4**) and (1*R*)-(–)-myrtenol (**8**), two naturally occurring monoterpenoids were selected, which are commercially available, cheap starting materials.

Results and Discussion

Synthesis of regioisomeric oxazolidinones from (1*S*)-(–)-α-pinene (4) and (1*R*)-myrtenol (8)

The synthesis of isopinocarveol (**5**), the key intermediate allylic alcohol, was performed according to a literature procedure with good yield.[34] The first step was the stereoselective epoxidation of (–)-α-pinene **4** carried out with *meta*-chloroperoxybenzoic acid (MCPBA) followed by base-catalysed allylic rearrangement applying aluminium isopropoxide ($Al(OiPr)_3$). The resulting allylic alcohol **5** was reacted with trichloroacetyl isocyanate followed by alkaline treatment delivering carbamate **6** with modest yield.[27,28,35] In the next step, aminohydroxylation was accomplished by potassium osmate(VI) catalyst and *t*-BuOCl in the presence of DIPEA affording oxazolidine-2-one **7**.[27] The reaction was found to be highly stereoselective giving exclusively the *diexo*-fused tricyclic **7** ring system (Scheme 1).



Scheme 1: Stereoselective synthesis of pinane-fused oxazolidin-2-one **7**.

The relative configuration of **7** was determined by 2D NMR technics. Clear NOE signals were observed between the H-7a and Me-10 as well as the H_a-9 and Me-10 protons. Beside NOESY experiments, the structure was also elucidated by X-ray crystallography (Figure 2).

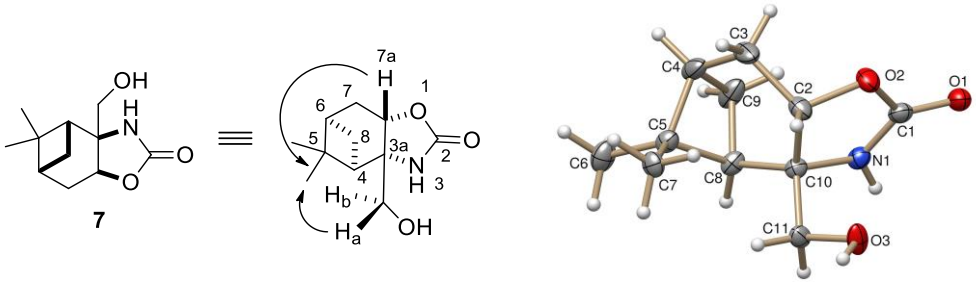
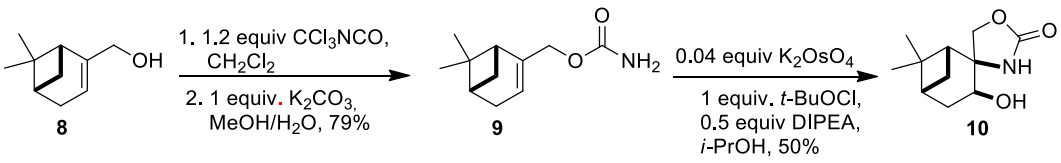


Figure 2: NOESY experiments and X-ray structure elucidation of oxazolidin-2-one **7**.

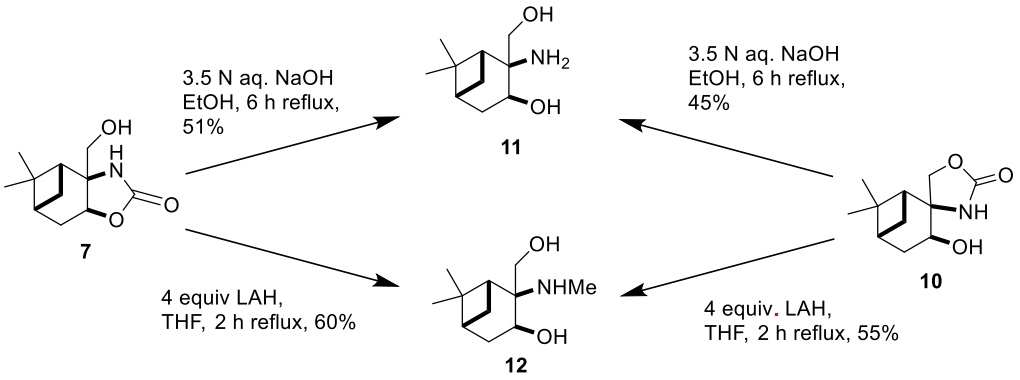
To synthesise regioisomeric spiro-oxazolidinone derivative **10**, (1*R*)-(–)-myrtenol (**8**) was chosen as starting material (Scheme 2). The synthesis method was similar to that mentioned above for (–)-isopinocarveol. In the first step, carbamate **9** was prepared,[36] then aminohydroxylation was carried out catalysed by potassium osmate(VI), which led to the formation of spiro-oxazolidine-2-one **10** in a highly regio- and stereoselective manner. Based on the NMR measurements of the crude product, spiro derivative **10** was obtained exclusively with relative configuration depicted on Scheme 2. Beside 2D NMR studies, the relative configuration of **10** was determined by the transformation of **10** to the corresponding aminodiols and comparing the products with those obtained from regioisomer **7** (discussed on Scheme 3).



Scheme 2: Stereoselective synthesis of pinane spiro-fused oxazolidin-2-one **10**.

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

To obtain a library of pinane-based 2-amino-1,3-diols, oxazolidine-2-ones **7** and **10** were applied as starting materials. Alkaline hydrolysis of both **7** and **10** resulted in the same primary aminodiol **11**.[37] 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 **7** was clarified by NMR and X-ray crystallographic results, we were able to assign the stereochemistry of spiro derivate **10** too. In a similar manner, $LiAlH_4$ (LAH) reduction of both **7** and **10** gave the same *N*-methylaminodiol **12** with modest yield (Scheme 3).

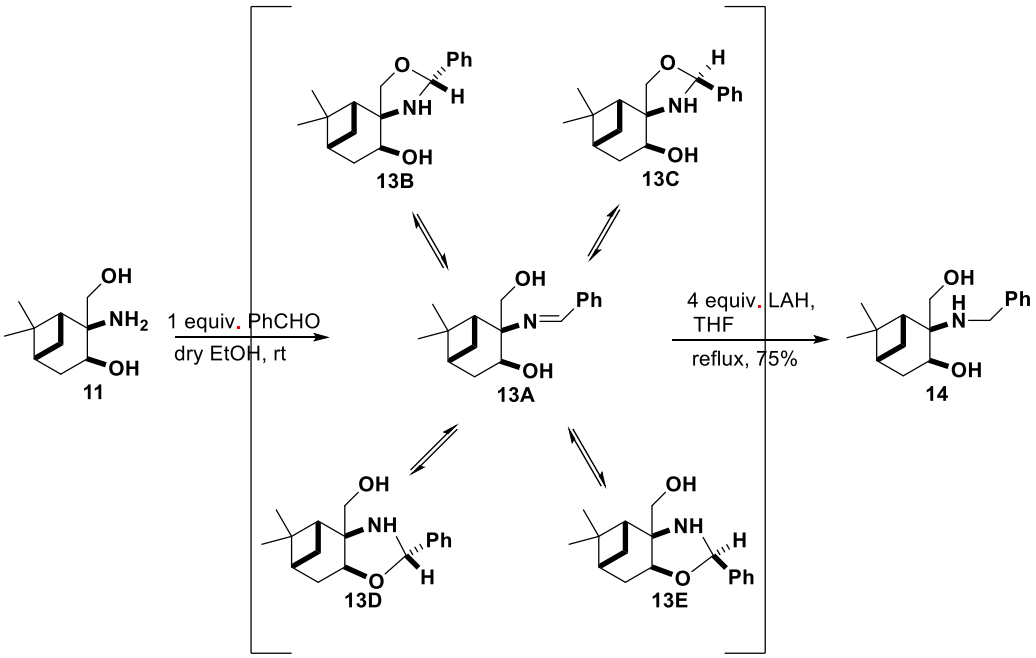


Scheme 3: Parallel synthesis of 2-amino-1,3-diols.

Subsequently, **11** was reacted with benzaldehyde. In this process, Schiff base **13A** was generated *in situ*. Our efforts to reduce it with sodium borohydride failed, since we did not observe the formation of the expected *N*-benzylaminodiol either at room temperature or under reflux conditions. ^{1}H-NMR and 2D NMR (NOESY and HMBC) measurements in $CDCl_3$ clearly show that the crude product was a five-component tautomeric mixture containing condensed oxazolidine **13E** as the main component. Additional minor components included the other condensed oxazolidine (**13E**), spiro compounds **13B** and **13C** as well as Schiff-base **13A** existing in a ratio of **13A**:**13B**:**13C**:**13D**:**13E** = 4:<1:4:12:79 (Scheme 4).[38,39] Since this finding is quite

unusual in the case of Schiff bases, we decided to study the ring/chain tautomeric mixture (**13A–E**) in the reaction of **7** with benzaldehyde by ^{1}H-NMR spectroscopy. When a time-dependent ^{1}H-NMR 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 **13E** can account for the difficulty of the reduction process and the necessity to use a stronger reducing agent and more sever conditions.

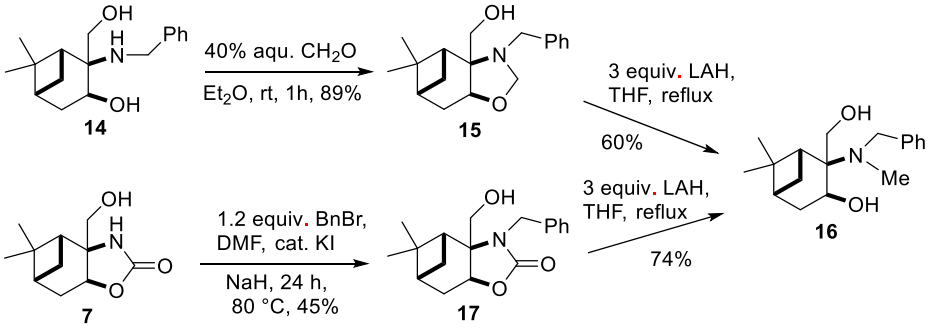
The reduction step, therefore, was performed by applying LAH a stronger reducing agent and an elongated time of reflux resulting in **14** (Scheme 4).



Scheme 4: Synthesis of *N*-benzyl-2-amino-1,3-diol **14**.

When **14** was treated with formaldehyde at room temperature, pinane-fused oxazolidine **15** was obtained regioselectively, in contrast to the results observed in the case of regioisomeric 3-amino-1,2-diols, where spiro-oxazolidines formed exclusively.[40] The relative configuration of **15** was determined by 2D NMR technics. Clear NOE signals were observed between the H-7a and Me-10 as well as the H_a-9

and Me-10 protons. In addition to NOESY experiments, the structure was also elucidated by X-ray crystallography (Figure 3).



Scheme 5: Synthesis of 2-amino-1,3-diols.

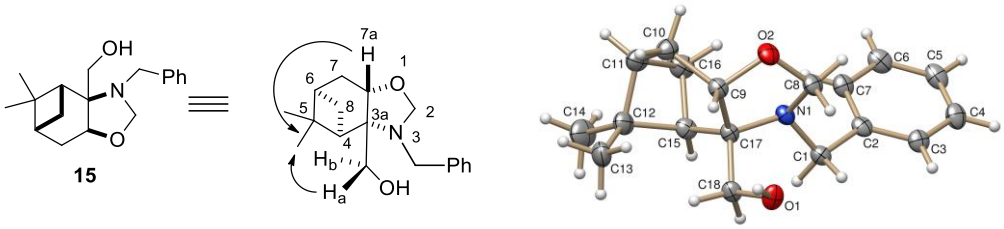
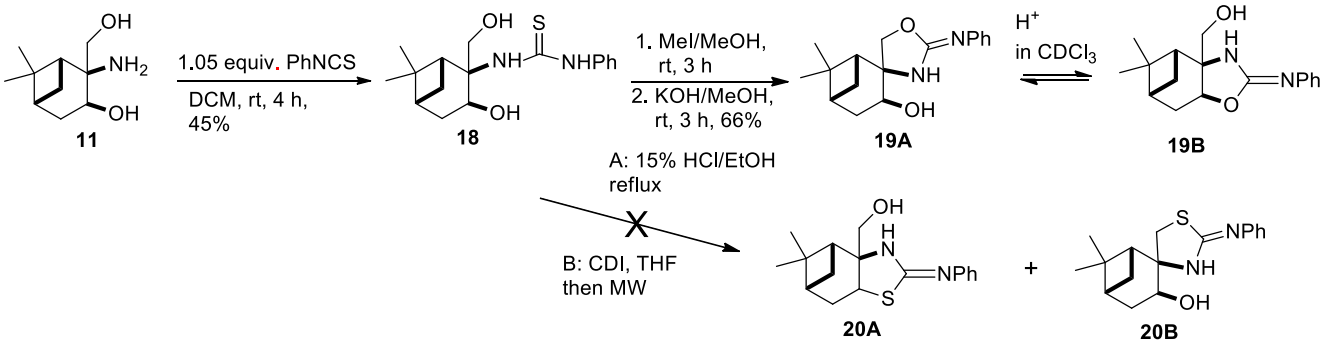


Figure 3: NOESY experiments and X-ray structure proofment of the structure of oxazolidine **15**.

LAH reduction of oxazolidine **15** gave *N*-benzyl, *N*-methyl analogue **16** which, alternatively, was prepared directly from 2-oxazolidinone **7** via *N*-benzylation followed by LAH reduction in 2 steps.

When **11** was reacted with phenylisothiocyanate, thiourea **18** was obtained, which underwent regioselective ring closure resulting in **19A**. It is important to mention that this regioselectivity is the opposite to that observed in the reaction of aminodiols **11** and **14** with aldehydes (see Schemes 4 and 5), but it is similar to that observed in our earlier study with pinane-based 3-amino-1,2-diols.[40] During the NMR study of **19A** in $CDCl_3$ for 30 days, an unknown slow ring–ring tautomerisation was observed,

forming a 1:1 mixture of two regioisomers **19A** and **19B**. Compound **19B** could be isolated from the mixture by column chromatography in pure form.



Scheme 6: Synthesis of 2-phenyliminooxazolidines.

The synthesis of heteroanalogue 2-phenyliminothiazolidines **20A** and **20B** 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 **19A** and **19B** is presented in Figure 4 and it explains why the acidic environment (present generally in $CDCl_3$ solution) is necessary. In a similar manner, oxazolidine–1,3-oxazine tautomerism of pulegone-based 3-amino-1,2-diols was recently reported.[31] When compound **19A** or **19B** were treated in less protic solvents such as DMSO-d6 or CD_3OD, tautomerisation was not observed.

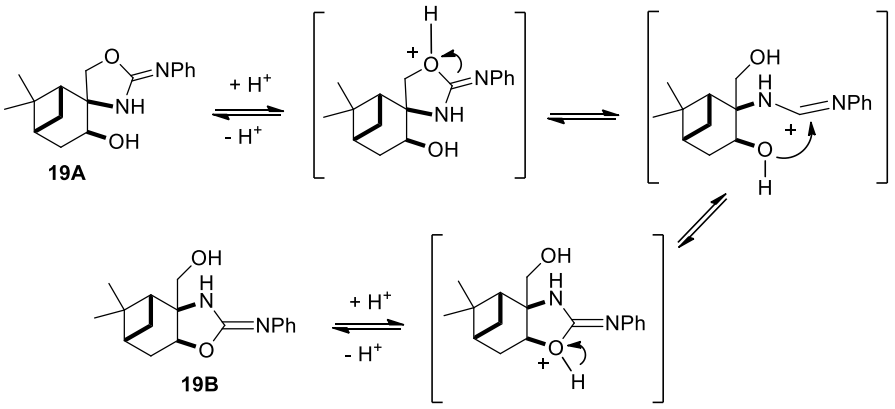


Figure 4: Proposed pathway for ring–ring tautomerism.

Conclusion

A library of pinane-based 2-amino-1,3-diols was synthesised in a stereoselective manner starting from (1*R*)-(–)-myrtenol and isopinocarveol prepared from α-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 and X-ray technics. The resulting primary and secondary 2-amino-1,3-diols underwent regioselective ring closure with formaldehyde and benzaldehyde producing pinane-condensed oxazolidines. In the case of 2-phenyliminooxazolidine, interesting ring–ring tautomerism was observed in $CDCl_3$.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 400 or Bruker Avance DRX 500 spectrometer [δ= 0 (TMS)] (Bruker Corp., Billerica, MA, USA) in 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 Ser II Elemental Analyzer (PerkinElmer Inc., Waltham, MA, USA). HRMS flow injection analysis was performed with Thermo Scientific Q Exactive Plus hybrid quadrupole-Orbitrap (Thermo Fisher Scientific, Waltham, MA, USA) mass spectrometer coupled to a Waters Acquity I-Class UPLC™ (Waters, Manchester, UK). Optical rotations were measured 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. (1*R*)-

(–)-Myrtenol (**8**) (*ee* > 95%) and (1*S*,5*S*)-(–)-(α)-pinene (*ee* > 95%) were obtained from Merck Hungary Co. Isopinocarveol (**5**) was prepared from commercially available (1*S*,5*S*)-(–)-(α)-pinene using a literature method,[29] with all spectroscopic data and physical properties similar to those reported therein.

General procedure for carbamate formation

Trichloroacetyl isocyanate (6.78 g, 36 mmol) was added dropwise to a solution of the allylic alcohol (4.5 g, 30 mmol) in dry DCM (50 mL) at 0 °C. After stirring for 2 h, the mixture was concentrated under reduced pressure and the residue was dissolved in MeOH (60 mL). Aqueous solution of K_2CO_3 (4.3 g in 15 mL of H_2O) was added to the solution at 0 °C and the mixture was allowed to stir for 4 h (TLC monitoring). MeOH was evaporated under reduced pressure and the aqueous residue was extracted with DCM (3 × 50 mL). The combined organic phase was dried (sicc. Na_2SO_4), filtered and concentrated under reduced pressure to yield the crude carbamate, which was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 9/1).

(1*R*,3*S*,5*R*)-6,6-Dimethyl-2-methylenebicyclo[3.1.1]heptan-3-yl carbamate (6)

Compound **6**: synthesis was performed starting from (–)-isopinocarveol, 4.18 g (71%), white crystalline powder, mp: 113–115 ^oC, $[\alpha]_D^{20}$ = +12.5 (c = 0.315, MeOH), ^1H NMR (500.2 MHz, $CDCl_3$): δ = 0.69 (s, 3H), 1.28 (s, 3H), 1.55 (d, 1H, *J* = 10.2 Hz), 1.86 (dd, 1H, *J* = 3.9, 15.3 Hz), 1.96-2.06 (m, 1H), 2.35-2.46 (m, 2H), 2.53 (t, 1H, *J* = 5.5 Hz), 4.75 (br s, 2H), 4.91 (s, 1H), 5.11 (s, 1H), 5.44 (d, 1H, *J* = 8.1 Hz), ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 22.0, 25.9, 27.9, 33.4, 39.6, 40.5, 50.8, 69.4, 114.0, 150.5, 156.8. Anal. calcd for $C_{11}H_{17}NO_2$ (195.26): C, 67.66; H, 8.78; N, 7.17; Found: C, 67.42; H, 8.36; N, 7.52. HRMS-ESI [M+H]+m/z calcd for $C_{11}H_{18}NO_2$: 196.13375, found 196.13321.

((1*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl carbamate (9)

Compound **9**: synthesis was performed starting from (1*R*)-(–)-myrtenol, 4.65 g (79%), white crystals, all physical and chemical properties are similar to those reported in the literature,[36] $[\alpha]_D^{20}$ = –43 (c = 0.265, MeOH), Anal. calcd for $C_{11}H_{17}NO_2$ (195.26): C, 67.66; H, 8.78; N, 7.17; Found: C, 67.42; H, 8.53; N, 7.35. HRMS-ESI [M+H]+m/z calcd for $C_{11}H_{18}NO_2$: 196.13375, found 196.13325.

General method for the aminohydroxylation process

To a solution of allylic carbamate **6** or **9** (2.00 g, 10.2 mmol) in *i*-PrOH (180 mL) freshly prepared 0.33% aqueous solution of NaOH (80 mL) was added. The solution was allowed to stir for 5 min, then freshly prepared *t*-BuOCl (1.026 mL, 10.3 mmol) was added. After stirring for 5 min, *N,N*-diisopropylethylamine (59 mg, 76.5 µL, 0.46 mmol) and potassium osmate(VI) dihydrate (135 mg, 0.37 mmol) were added to the solution in one portion. After the addition of 0.33% aqueous NaOH solution of (20 mL) the mixture was stirred for 24 h (TLC monitoring) then quenched with Na_2SO_3 (500 mg) and allowed to stir for 30 min. The mixture was extracted with EtOAc (3 × 50 mL), and the organic layer was washed with brine (1 × 50 mL), dried (sicc. Na_2SO_4), filtered and concentrated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 1/2).

(3a*S*,4*R*,6*R*,7a*S*)-3a-Hydroxymethyl-5,5-dimethylhexahydro-4,6-methanobenzo[*d*]oxazol-2(3*H*)-one (7)

Compound **7**: 0.86 g (40%), white crystalline powder, mp: 195–197 °C, $[\alpha]_D^{20}$ = +31 (c = 0.290, MeOH), ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.80 (s, 3H), 1.00-1.10 (m, 1H), 1.20 (s, 3H), 1.33 (d, 1H, *J* = 9.9 Hz), 1.58 (dt, 1H, *J* = 3.6, 14.1 Hz), 1.81-1.87 (m, 1H),

1.99 (t, 1H, *J* = 5.8 Hz), 2.08-2.16 (m, 1H), 2.26-2.33 (m, 1H), 3.97-4.02 (m, 1H), 4.03 (d, 1H, *J* = 8.6 Hz), 4.16 (d, 1H, *J* = 8.6 Hz), 5.07 (d, 1H, *J* = 5.0 Hz), 7.69 (br s, 1H), ^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.4, 27.2, 27.4, 37.3, 38.6, 39.8, 53.0, 65.6, 68.9, 76.8, 158.4. Anal. calcd for $C_{11}H_{17}NO_3$ (211.26) : C, 62.54; H, 8.11; N, 6.63; Found: C, 62.28; H, 8.47; N, 6.23. HRMS-ESI [M+H]+m/z calcd for $C_{11}H_{18}NO_3$: 212.12867, found 212.12812.

(3a*S*,4*R*,6*R*,7a*S*)-3a-Hydroxymethyl-5,5-dimethylhexahydro-4,6-methanobenzo[*d*]oxazol-2(3*H*)-one (10)

Compound **10**: 1.08 g (50%), white crystalline powder, mp: 153–156 ^{o}C, $[\alpha]_D^{20}$ = –55 (c = 0.285, MeOH), ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.80 (s, 3H), 1.20 (d, 1H, *J* = 11.1 Hz), 1.23 (s, 3H), 1.75-1.83 (m, 2H), 1.85-1.90 (m, 1H), 2.21-2.28 (m, 1H), 2.30-2.38 (m, 1H), 3.21 (dd, 1H, *J* = 5.7, 11.5 Hz), 3.41 (dd, 1H, *J* = 5.8, 11.7 Hz), 4.64 (d, 1H, *J* = 8.1 Hz), 5.05 (t, 1H, *J* = 5.8 Hz), 7.43 (br s, 1H), ^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.3, 26.7, 27.3, 34.8, 38.5, 39.4, 65.7, 65.8, 71.4, 158.1. Anal. calcd for $C_{11}H_{17}NO_3$ (211.26) : C, 62.54; H, 8.11; N, 6.63; Found: C, 62.36; H, 8.27; N, 6.41. HRMS-ESI [M+H]+m/z calcd for $C_{11}H_{18}NO_3$: 212.12867, found 212.12817.

General method for the alkaline hydrolysis of oxazolidinones

To a solution of oxazolidinone **7** or **10** (1.7 g, 8.0 mmol) in dry EtOH (21 mL), 14% aqueous solution of NaOH (10 mL) was added and the mixture was treated under reflux condition for 6 h. The solution was evaporated to approx. 10 mL volume then extracted with DCM (3 × 30 mL). The combined organic layer was dried (sicc. Na_2SO_4), filtered and concentrated under reduced pressure to yield crude product **12**, which was purified as hydrochloride salt by recrystallisation form an EtOH/Et_2O mixture.

(1*R*,2*S*,3*S*,5*R*)-2-Amino-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-3-ol hydrochloride (11)

Compound **11**: 0.91 g (51%) from 10 and 0.80 g (45%) from **11**, white crystalline powder, mp: 195–196 ^{o}C, $[\alpha]_D^{20}$= +7 (c = 0.270, MeOH), ^{1}H NMR (400 MHz, DMSO-d_6): δ= 0.92 (s, 3H), 1.23 (s, 3H), 1.50 (d, 1H, *J* = 10.6 Hz), 1.68-1.75 (m, 1H), 1.84-1.89 (m, 1H), 2.13-2.20 (m, 1H), 2.27 (t, 1H, *J* = 5.5 Hz), 2.31-2.37 (m, 1H), 3.43 (dd, 1H, *J* = 4.8, 11.6 Hz), 3.61 (dd, 1H, *J* = 5.6, 11.7 Hz), 3.99 (dd, 1H, *J* = 5.2, 9.0 Hz), 5.48 (t, 1H, *J* = 5.5 Hz), 5.64 (br s, 1H), 7.65 (br s, 3H), ^{13}C NMR (400 MHz, DMSO-d_6): δ= 24.3, 27.1, 27.7, 37.7, 39.2, 40.4, 45.9, 63.3, 64.9. Anal. calcd for $C_{10}H_{20}ClNO_2$ (221.72): C, 54.17; H, 9.09; N, 6.32; Found: C, 54.43; H, 9.27; N, 6.45. HRMS-ESI [M+H]+m/z calcd for $C_{10}H_{20}NO_2$: 186.14940, found 186.14886.

General method for the LAH reduction of oxazolidinones 7 and 10

To the stirred suspension of $LiAlH_4$ (0.25 g, 6.6 mmol) in dry THF (5 mL) the solution of **7** or **10** (0.35 g, 1.67 mmol) in dry THF (5 mL) was added dropwise under ice cooling. The reaction mixture was treated under reflux conditions for 2 h, then the mixture of H_2O (0.50 mL) and THF (5 mL) was added dropwise with cooling. After 30 min stirring, the inorganic material was filtered off and washed with THF (3 × 30 mL). The filtrate was dried (sicc. Na_2SO_4), filtered and evaporated. The obtained crude product was purified by column chromatography on silica gel (toluene/EtOH = 1/1).

(1*R*,2*S*,3*S*,5*R*)-2-Hydroxymethyl-6,6-dimethyl-2-methylaminobicyclo[3.1.1]heptan-3-ol (12)

Compound **12**: 0.17 g (60%) from **7** and 0.19 g (55%) from **10**, white crystalline powder, mp: 126–128 ^{o}C, $[\alpha]_D^{20}$= –3 (c = 0.200, MeOH), ^{1}H NMR (400 MHz, $CDCl_3$): δ= 0.91 (s, 3H), 1.21 (s, 3H), 1.45 (d, 1H, *J* = 9.3 Hz), 1.50-1.56 (m, 1H), 1.77-1.81 (m, 1H), 1.83-1.87 (m, 1H), 2.02-2.06 (m, 1H), 2.08 (s, 3H), 2.26-2.33 (m, 1H), 3.22 (d, 2H, *J* = 11.0 Hz), 3.35 (d, 1H, *J* = 11.2 Hz), 4.01 (dd, 1H, *J* = 5.7, 9.1 Hz), ^{13}C NMR (400 MHz, $CDCl_3$): δ= 24.9, 27.6, 28.1, 28.8, 38.4, 38.8, 40.4, 46.6, 61.5, 64.8, 66.8. Anal. calcd for $C_{11}H_{21}NO_2$ (199.29): C, 66.29; H, 10.62; N, 7.03; Found: C, 66.53; H, 10.27; N, 7.33. HRMS-ESI [M+H]+m/z calcd for $C_{11}H_{22}NO_2$: 200.16505, found 200.16451.

Preparation of 13A–E tautomeric mixture

Aminodiol **11** (20 mg, 0.1 mmol) and benzaldehyde (10 µl, 10.6 mg, 1 mmol) were dissolved in dry ethanol (2 mL) and stirred for 2 h at room temperature, then the solvent was evaporated under reduced pressure to afford the mixture of **13A–E** examined in $CDCl_3$.

Compounds **13A–E**: 0.020 g (98%) crude mixture. Ratio of **13A**:**13B**:**13C**:**13D**:**13E**: 4:<1:4:12:79 based on ^{1}H-NMR and 2D NMR (NOESY and HMBC) measurement. Characteristic chemical shifts for the C-2 methyne peaks of tautomers: ^{1}H NMR (500.2 MHz, $CDCl_3$): δ= 8.02 (d, *J* = 6.5 Hz): **13A**, 5.90 (s): **13B**/**13C**, 5.41 (s): **13D**, 5.30 (s): **13E**.

(1*R*,2*S*,3*S*,5*R*)-2-Benzylamino-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-3-ol (14)

To a solution of aminodiol **11** (liberated base) (0.60 g, 3.2 mmol) in dry ethanol (20 mL) benzaldehyde (0.35 g, 0.33 mL, 3.3 mmol) was added in one portion, and the solution was stirred at room temperature for 1 h and then evaporated to dryness. The residue

was dissolved in dry THF (3 mL) and then added dropwise to the stirred suspension of dry THF (10 mL) and $LiAlH_4$ (0.49 g, 12.8 mmol). The reaction mixture was treated under reflux conditions for 3 h, then the mixture of H_2O (1.00 mL) and THF (8 mL) was added dropwise with cooling. After stirring for 30 min, the inorganic material was filtered off and washed with THF (3 × 30 mL). The filtrate was dried (sicc. Na_2SO_4), filtered and evaporated. The obtained crude product was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 9/1).

Compound **14**: 0.66 g (75%), white crystalline powder, mp: 112–114 °C, $[\alpha]_D^{20}$= +10.8 (c = 0.320, MeOH), ^{1}H NMR (400 MHz, DMSO-d_6): δ= 0.95 (s, 3H), 1.24 (s, 3H), 1.57 (dd, 1H, *J* = 5.5, 13.6 Hz), 1.65 (d, 1H, *J* = 9.5 Hz), 1.80-1.85 (m, 1H), 1.98 (t, 1H, *J* = 5.7 Hz), 2.07-2.14 (m, 1H), 2.28-2.35 (m, 1H), 3.30-3.33 (m, 2H, overlapped with H_2O peak), 3.48 (d, 1H, *J* = 10.9 Hz), 3.65 (d, 1H, *J* = 12.4 Hz), 4.11 (dd, 1H, *J* = 6.4, 8.6 Hz), 4.32 (br s, 1H), 7.18-7.37 (m, 5H), ^{13}C NMR (400 MHz, DMSO-d_6): δ= 25.0, 27.9, 29.0, 38.5, 38.7, 40.5, 45.3, 47.1, 47.4, 61.9, 66.0, 67.1, 126.9, 128.5, 128.6, 142.4. Anal. calcd for $C_{17}H_{25}NO_2$ (275.39): C, 74.14; H, 9.15; N, 5.09; Found: C, 74.47; H, 9.31; N, 5.35. HRMS-ESI [M+H]+m/z calcd for $C_{17}H_{26}NO_2$: 276.19635, found 276.19581.

((3a*S*,4*R*,6*R*,7a*S*)-3-Benzyl-5,5-dimethyloctahydro-4,6-methanobenzo[d]oxazol-3a-yl)methanol (15)

To the solution of **14** (0.25 g, 0.9 mmol) in Et_2O (10 mL), 40% aqueous formaldehyde solution (4 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 (5 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layer was washed with saturated NaCl solution (2 × 20 mL) then dried (sicc. Na_2SO_4), filtered and

evaporated to dryness. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 3/2).

Compound **15**: 0.23 g (89%), pale-yellow crystalline powder, mp: 77–78 ^{o}C, $[\alpha]_D^{20}$ = +3 (c = 0.285, MeOH), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (s, 3H), 1.30 (s, 3H), 1.45 (d, 1H, *J* = 10.2 Hz), 1.86-1.95 (m, 2H), 2.08-2.14 (m, 1H), 2.35-2.43 (m, 1H), 2.48-2.55 (m, 1H), 3.27 (br d, 1H, *J* = 9.5 Hz), 3.60 (br d, 1H, *J* = 10.9 Hz), 3.67 (br d, 1H, *J* = 13.7 Hz), 3.86 (br d, 1H, *J* = 12.5 Hz), 4.44 (s, 1H), 4.50 (d, 1H, *J* = 2.8 Hz), 4.56 (d, 1H, *J* = 8.6 Hz), 7.21-7.35 (m, 5H), ^{13}C NMR (400 MHz, $CDCl_3$): δ = 24.6, 27.2, 27.6, 35.7, 39.1, 47.0, 48.9, 65.3, 76.3, 84.5, 127.3, 128.1, 128.6, 139.6. Anal. calcd for $C_{18}H_{25}NO_2$ (287.40): C, 75.22; H, 98.77; N, 4.87; Found: C, 75.54; H, 98.39; N, 4.61. HRMS-ESI [M+H]+m/z calcd for $C_{18}H_{26}NO_2$: 288.19635, found 288.19581.

(1*R*,2*S*,3*S*,5*R*)-2-(*N*-Benzyl-*N*-methylamino)-2-hydroxymethyl-6,6 dimethylbicyclo[3.1.1]heptan-3-ol (16)

To the stirred suspension of $LiAlH_4$ (0.17 g, 4.38 mmol) in dry THF (5 mL) the solution of **15** or **17** (1.46 mmol) in dry THF (5 mL) was added dropwise at room temperature. After a 12-h treatment under reflux conditions the mixture of H_2O (0.30 mL) and THF (4 mL) was added dropwise with cooling to the reaction. After 30 min stirring, the inorganic material was filtered off and washed with THF (3 × 20 mL). The filtrate was dried (sicc. Na_2SO_4), filtered and evaporated. The obtained crude product was purified by column chromatography on silica gel (DCM/MeOH = 19/1).

Compound **16**: 0.25 g (60%) from **15**, 0.31 g (74%) from **17**, colourless oil, $[\alpha]_D^{20}$ = –40 (c = 0.365, MeOH), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (s, 3H), 1.35 (s, 3H), 1.75 (d, 1H, *J* = 10.5 Hz), 1.92-1.98 (m, 1H), 2.10-2.16 (m, 1H), 2.32-2.39 (m, 1H), 2.44-2.53 (m, 1H), 2.54 (s, 3H), 2.72 (t, 1H, *J* = 5.4 Hz), 3.79-3.84 (m, 1H), 3.87 (d, 1H, *J* = 12.8

Hz), 4.10 (d, 1H, *J* = 12.4 Hz), 4.12 (d, 1H, *J* = 12.4 Hz), 4.30 (br d, 1H, *J* = 11.7 Hz), 7.28-7.46 (m, 5H), ^{13}C NMR (400 MHz, $CDCl_3$): δ = 23.9, 26.3, 28.2, 37.1, 38.5, 38.8, 45.1, 57.3, 62.7, 64.1, 64.7, 128.3, 128.8, 129.9, 135.7. Anal. calcd for $C_{18}H_{27}NO_2$ (289.41): C, 74.70; H, 9.40; N, 4.84; Found: C, 74.38; H, 9.53; N, 4.65. HRMS-ESI [M+H]+m/z calcd for $C_{18}H_{28}NO_2$: 290.21200, found 290.21146.

(3a*S*,4*R*,6*R*,7a*S*)-3-Benzyl-3a-(hydroxymethyl)-5,5-dimethylhexahydro-4,6-methanobenzo[d]oxazol-2(3H)-one (**17**)

To a solution of **7** (0.30 g, 1.42 mmol) in DMF (10 ml), benzyl bromide (0.29 g, 0.200 mL, 1.7 mmol), $CsCO_3$ (0.30 g, 0.92 mmol) and a catalytic amount of KI (16 mg) were added and the mixture was stirred for 24 h at 80 °C. After cooling and filtrating off the solid, the solvent was evaporated under vacuum and the residual oily product was dissolved in the mixture of DCM (20 mL) and H_2O (20 mL). The aqueous phase was extracted with DCM (3 × 20 mL) and the combined organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The crude product was purified by column chromatography on silica gel (DCM/MeOH = 19/1).

Compound **17**: 0.19 g (45 %), yellow oil, $[\alpha]_D^{20}$ = –20 (c = 0.285, MeOH), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (s, 3H), 0.87 (d, 1H, *J* = 9.1 Hz), 1.12 (s, 3H), 1.71-1.81 (m, 4H), 2.33-2.41 (m, 1H), 3.44 (ddd, 2H, *J* = 5.7, 12.1, 23.8 Hz), 4.08 (d, 1H, *J* = 15.7 Hz), 4.38 (d, 1H, *J* = 15.7 Hz), 4.73 (d, 1H, *J* = 8.3 Hz), 5.12 (t, 1H, *J* = 5.1 Hz), 7.20-7.38 (m, 5H), ^{13}C NMR (400 MHz, $CDCl_3$): δ = 22.5, 27.2, 27.4, 35.1, 37.9, 39.2, 43.9, 45.4, 62.3, 69.7, 70.5, 127.5, 128.5, 128.8, 138.8, 158.2. Anal. calcd for $C_{18}H_{23}NO_3$ (301.38): C, 71.73; H, 7.69; N, 4.65, Found: C, 71.89; H, 7.48; N, 4.81. HRMS-ESI [M+H]+m/z calcd for $C_{18}H_{24}NO_3$: 302.17562, found 302.17507.

1-((1*R*,2*S*,3*S*,5*R*)-3-Hydroxy-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)-3-phenylthiourea (18)

To a solution of aminodiol **11** (70 mg, 0.377 mmol) in toluene (30 mL), 1.05 eq. of phenyl isothiocyanate (80 mg, 70 µl, 0.396 mmol) was added and the reaction mixture was stirred for 12 h at room temperature. After evaporation, the crude product was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 19/1).

Compound **18**: 85 mg (70%), white powder, mp: 168–170 °C, $[\alpha]_D^{20}$ = +134 (c = 0.275, MeOH), ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.02 (s, 3 H), 1.10-1.12 (d, 1H, *J* = 10.8 Hz), 1.29 (s, 3 H), 1.49-1.53 (m, 1H), 1.62 (s, 2H), 1.93-1.94 (m, 1H), 2.28-2.32 (m, 1H), 2.39-2.43 (m, 1H), 2.65 (s, 1H), 3.25-3.27 (t, 1H, *J* = 5.8 Hz), 3.67-3.69 (d, 1H, *J* = 11.1 Hz), 4.54-4.57 (t, 1H, *J* = 8.2 Hz), 4.91-4.93 (d, 1H, *J* = 10.9 Hz), 7.23-7.29 (m, 2H), 7.40-7.43 (m, 2H), 7.60 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 24.5, 28.6, 29.3, 36.2, 38.5, 40.2, 47.2, 66.0, 66.9, 68.4, 125.1, 127.3, 130.1, 136.4, 178.6. Anal. calcd for $C_{17}H_{24}N_2O_2S$ (320.45): C, 63.72; H, 7.55; N, 8.74; Found: C, 63.75; H, 7.53; N, 8.71. HRMS-ESI [M+H]+m/z calcd for $C_{17}H_{25}N_2O_2S$: 321.16367, found 321.16326.

(1*R*,2*S*,3*S*,5*R*)-6,6-Dimethyl-2'-(phenylimino)spiro[bicyclo[3.1.1]heptan-2,4'-oxazolidine]-3-ol (19A)

Thiourea **18** (56 mg, 0.174 mmol) was dissolved and stirred in the solution of methanol (5 mL) and MeI (5.5 eq., 63 µl, 0.957 mmol) at room temperature. After a 3-h stirring the solvent was evaporated and the residue was redissolved and stirred in 2 mL of 2.5 N methanolic potassium hydroxide for 12 h at room temperature. After evaporation of the solvent, the residue was dissolved in the mixture of H_2O (10 mL) and $CHCl_3$ (10 mL) and the aqueous phase was extracted with $CHCl_3$ (2 × 10 mL) and the organic

layer was dried (sicc. Na_2SO_4) and evaporated. The crude product was then purified by column chromatography on silica gel (*n*-hexane/EtOAc = 1/1).

Compound **19A**: 33 mg (66%), orange solid, mp: 138–140 °C, $[\alpha]_D^{20}$ = +13 (c = 0.335, MeOH), ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.85 (s, 3H), 1.26 (m, 3H), 1.73-1.75 (m, 1H), 1.91-1.95 (m, 1H), 1.96-1.99 (m, 1H), 2.02-2.05 (m, 1H), 2.22-2.27 (m, 1H), 2.39-2.44 (m, 1H), 3.93-3.96 (m, 1H), 4.16 (s, 2H), 6.99-7.02 (m, 1H), 7.26-7.29 (m, 2H), 7.40-7.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 23.4, 26.9, 27.6, 29.7, 37.5, 38.4, 40.3, 53.1, 70.1, 80.0, 118.6, 123.0, 129.1, 157.0. Anal. calcd for $C_{17}H_{22}N_2O_2$ (286.38): C, 71.30; H, 7.74; N, 9.78; Found: C, 71.33; H, 7.77; N, 9.81. HRMS-ESI [M+H]+m/z calcd for $C_{17}H_{23}N_2O_2$: 287.17595, found 287.18626.

((3a*S*,4*R*,6*R*,7a*S*)-5,5-dimethyl-2-(phenylimino)octahydro-4,6-methanobenzo[d]oxazol-3a-yl)methanol (19B)

From the $CHCl_3$ solution of **19A** (50 mg) standing for 30 days, both **19A** and **19B** tautomeric products were isolated by column chromatography on silica gel ($CHCl_3$/MeOH = 19/1)

Compound **19B**: 25 mg (50%), white solid, mp: 92–95 °C, $[\alpha]_D^{20}$ = +18 (c = 0.200, MeOH), ^{1}H NMR (400 MHz, $CDCl_3$) δ = 0.88 (s, 3H), 1.19-1.21 (d, 1H, *J* = 10.8 Hz), 1.30 (s, 3H), 1.92-1.93 (m, 1H), 2.01-2.04 (m, 1H), 2.13-2.16 (m, 1H), 2.30-2.34 (m, 1H), 2.42-2.46 (m, 1H), 3.59-3.66 (q, 2H, *J* = 11.1 26.9 Hz), 4.79-4.81 (d, 1H, *J* = 8.1 Hz), 7.01-7.04 (t, 1H, *J* = 7.1 Hz), 7.27-7.30 (t, 2H, *J* = 7.8 Hz), 7.37-7.38 (m, 2H), ^{13}C NMR (125 MHz, $CDCl_3$) δ = 24.5, 27.1, 27.3, 30.0, 34.5, 38.7, 39.3, 47.7, 68.0, 75.4, 119.1.4, 123.3, 129.4, 139.0, 156.6. Anal. calcd for $C_{17}H_{22}N_2O_2$ (286.38): C, 71.30; H, 7.74; N, 9.78; Found: C, 71.11; H, 7.67; N, 9.93. HRMS-ESI [M+H]+m/z calcd for $C_{17}H_{23}N_2O_2$: 287.17595, found 287.18612.

X-Ray structure determinations

The crystals of **7** and **15** were immersed in cryo-oil, mounted in a loop, and measured at a temperature of 120 K. The X-ray diffraction data were collected on a Rigaku Oxford Diffraction Supernova diffractometer using Cu Kα radiation. The *CrysAlisPro*[41] software package was used for cell refinements and data reductions. A multi-scan (**7**) or an analytical absorption correction (**15**) was applied to the intensities before structure solutions by using *CrysAlisPro*[41] software. The structures were solved by intrinsic phasing (*SHELXT*[42]) method. Structural refinements were carried out using SHELXL[43] software with *SHELXLE*[44] graphical user interface. The NH and OH hydrogen atoms were located from the difference Fourier map and refined isotropically. All other hydrogen atoms were positioned geometrically and constrained to ride on their parent atoms, with C–H = 0.95-1.00 Å and U_{iso} = 1.2–1.5 U_{eq}(parent atom). The crystallographic details are summarised in Table **S1** (Supporting Information, S33).

Supporting Information

Supporting Information File 1: analytical data, NMR spectra and X-data of the prepared compounds.

File Name: Belstein_2021_supporting_Szakonyi

File Format: docx

Title: Supporting information for “Synthesis and transformation of sphingosine analogue pinane-based 2-amino-1,3-diols”

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