Synthesis of enantiomeric spirooxazolines and spirooxazolidines by the regioselective ring closure of (−)-α-pinene-based aminodiols

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Dedicated to Professor Csaba Szántay on the occasion of his 80th birthday

Abstract
Starting from (1R,2S,3S,5R)-2-benzylaminomethyl-6,6-dimethylbicyclo[3.1.1]heptane-2,3-diol (4) and (1R,2S,3S,5R)-2-aminomethyl-6,6-dimethylbicyclo[3.1.1]heptane-2,3-diol (5), spirooxazolines and spirooxazolidines were prepared. In the reactions of 4 and 5 with alkyl or aryl isothiocyanate, the ring closure proceeded regioselectively and resulted only in spiro derivatives of 2-aryl- and alkyliminooxazolidines 12-17. The primary aminodiol 5 was transformed with ethyl 4-chlorobenzimidate to a spiro-2-(4-chlorophenyl)oxazoline 18 in a highly regioselective ring closure. The reaction of 5 with formaldehyde resulted in tetracyclic compound 19.

Keywords: Monoterpene, chiral, aminodiol, regioselective reaction, oxazolidine, oxazoline

Introduction

Aliphatic aminodiols play important roles in drug therapy and drug research.1−7 For example, some have been found to act as HIV protease inhibitors1−3 and still others have been shown to exert renin inhibitor activity.5,6 Aminodiols are also useful starting materials for the syntheses of oxazines or oxazolidines, depending upon which hydroxy group undergoes ring closure with the amino group.8 Since the resulting heterobicycles contain a free hydroxy group, further ring closure can yield more complex heterocyclic structures. Additionally, alicyclic aminodiols are potentially excellent starting points for the development of new ring−chain tautomeric systems.8 Further, enantiomeric oxazolines and 1,3-oxazines have proved to be extremely efficient ligands in the asymmetric catalysis of a wide range of enantioselective syntheses.9 Chiral phosphine-oxazine ligands and phosphate-oxazolidine ligands were recently successfully used in palladium-catalyzed asymmetric allylic alkylation.10−13
Besides the chemical interest, several of these heterocyclic aminodiol systems exhibit noteworthy biological activity, e.g. cytoxazone, a selective modulator of T\(_{H2}\) cytokine secretion, which is a microbial metabolite isolated from *Streptomyces* species.\(^{14,15}\)

As a continuation of our research on monoterpene-based β-amino acid derivatives, such as amino esters and amino alcohols, which have proved to be excellent building blocks for the syntheses of monoterpene-fused saturated 1,3-heterocycles,\(^{16-19}\) we recently reported syntheses of enantiomerically pure pinane-based aminodiol enantiomers, which were applied as chiral auxiliaries in enantioselective reactions of diethyl zinc with aromatic aldehydes.\(^{20}\) In the present work, our aim was to study the regioselectivity of the ring closure of aminodiols readily available in 4 steps from (-)-\(\alpha\)-pinene.

**Results and Discussion**

The starting enantiomeric aminodiols 4 and 5 were synthesized stereoselectively by a method described earlier. Starting from commercially available (-)-\(\alpha\)-pinene 1, epoxidation was follows by rearrangement of the \(\alpha\)-pinene oxide to *trans*-pinocarveol 2, which was converted with MCPBA to epoxylcohol 3 in a stereospecific reaction.\(^{21-23}\) Secondary aminodiol 4 was obtained by the reaction of 3 with benzylamine. Primary aminodiol 5 was prepared from 4 via debenzylation under standard conditions, by hydrogenation in the presence of palladium-on-carbon catalyst (Scheme 1).\(^{20}\)

![Scheme 1](image)

Scheme 1. (i) MCPBA, DCM, rt, 6 h, 82%; (ii) Al(OiPr)\(_3\), toluene, reflux, 2 h, 70%; (iii) MCPBA, DCM, Na\(_2\)HPO\(_4\) buffer, rt, 12 h, 60%; (iv) 4 equiv. PhCH\(_2\)NH\(_2\), 1 equiv. LiClO\(_4\), MeOH, reflux 3 days 63%; (v) 10% Pd/C, MeOH, H\(_2\), 1 atm, 95%.

In order to assess the tendencies of aminodiols 4 and 5 to furnish either a monoterpene spirooxazolidine or a monoterpene-condensed 1,3-oxazine ring, 4 and 5 were treated with phenyl, \(m\)-methoxyphenyl and ethyl isothiocyanates, which afforded the corresponding thiourease derivatives 6-11. After reaction with methyl iodide followed by treatment with base (KOH), these adducts underwent ring closure via methyl mercaptan elimination.\(^{8,16,24}\) The spirooxazolidine derivatives 12-17 were readily identified as the sole products in each respective case (Scheme 2).
Scheme 2. (i) 1.05 equiv. R²NCS, toluene, rt, 1-3 h, 75-90%; (ii) 5.3 equiv. MeI, MeOH, 6 h, rt; (iii) 2.5 M KOH/MeOH, rt, 4 h, 65-90%.

For testing, the most stable structures formed for 12 and 15 were geometry optimized for both a monoterpane spirooxazolidine and a monoterpane-condensed 1,3-oxazine ring. Final minimizations were carried out by using Density functional theory (DFT) quantum mechanical method at the B3LYP/6-31G* level in vacuum.²⁵ The DFT structures converged to the corresponding local minimum of the potential energy surface. The isomeric energy differences between the (–)–α-pinene derived spirooxazolidines (e.g. 12 and 15) and the corresponding 1,3-oxazines (e.g. 18 and 19) proved that oxazolidines are more stable than 1,3-oxazines, as shown in Figure 1.

Figure 1. The isomeric energy difference between the spirooxazolidines (12 and 15) and 1,3-oxazines (18 and 19); $E_{12} - E_{18} = -10.58$ kcal/mol; $E_{15} - E_{19} = -7.18$ kcal/mol.
The spirooxazolidine derivatives 12-17 and 20 were also distinguished from the 1,3-oxazines by the characteristic $^{13}$C chemical shifts of C-3, C-4' and C-5' and by 2D heteronuclear NMR experiments. In the HMBC spectra, correlations between the C-3 proton and C-2’ were not observed, implying that the products of the ring closure of thiourea derivatives 6-11 were spirooxazolidines.\(^8\)

Another typical reaction of 1,2- and 1,3-aminoalcohols is their ring closure with imidates, resulting in 2-aryl- or 2-alkyl-substituted oxazolines or dihydro-1,3-oxazines. These 1,3-heterocycles are catalysts often applied in enantioselective transformations, e.g. in palladium-catalyzed asymmetric allylic alkylations. Starting from primary aminodiol 5, the ring closure with ethyl 4-chlorobenzimidate resulted in spirooxazoline 20 in a regioselective reaction (Scheme 3).

\[
\begin{align*}
&\text{20} &\text{5} &\text{21} &\text{Scheme 3. (i) 4-ClC}_6\text{H}_4\text{C}(=\text{NH})\text{OEt, EtOH, cat. AcOH, reflux, 8 h, 55%; (ii) CH}_2\text{O/H}_2\text{O, 4 h, rt, 60%}.}
\end{align*}
\]

Since the former reactions clearly demonstrated that formation of the spiro compound is preferable relative to the fused system, we applied formaldehyde for the ring closure to lead the secondary hydroxy group into a ring closure procedure. When aminodiol 5 was treated with formaldehyde solution, tetracyclic compound 21 was obtained. The first step is probably formation of the corresponding spiro compound, followed by conversation to 1,3-oxazine 21.

**Experimental Section**

**General Procedures.** $^1$H NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer (400 MHz, $\delta$=0 (TMS), in CDCl$_3$ or in DMSO-d6. Chemical shifts are expressed in ppm ($\delta$) relative to TMS as internal reference. $J$ values are given in Hz. FT-IR spectra were recorded on an AVATAR 330 FT-IR spectrometer (Thermo Nicolet, USA). Microanalyses were performed on a Perkin-Elmer 2400 elemental analyzer. GC measurements were made on a Perkin-Elmer Autosystem XL GC, consisting of a Flame Ionization Detector and a Turbochrom Workstation data system (Perkin-Elmer Corporation, Norwalk, USA). The column used for the direct separation of enantiomers was a CHIRASIL-DEX CB column (2500x0.25 mm I.D.). Optical rotations were obtained with a Perkin-Elmer 341 polarimeter. Melting points were determined on a Kofler apparatus and are uncorrected. The
preparations of aminodiols 4 and 5 from (1S,5S)-(−)-α-pinene were performed by a literature method.\textsuperscript{20}

**General procedure for the preparation of thiourea derivatives 6-11**

Ethyl, phenyl or 3-methoxyphenyl isothiocyanate (1.70 mmol) was added to a solution of the appropriate aminodiol 4 or 5 (1.62 mmol) in toluene (15 mL), and the resulting solution was stirred at room temperature. When the reaction was complete, as indicated by TLC (1-3 h), the solvent was removed under reduced pressure. The resulting crude crystalline products were recrystallized from EtOAc–iPr\textsubscript{2}O, while oily products were purified by column chromatography on silica gel with a toluene:n-hexane = 9:1 mixture.

1-Benzyl-1-[(2,3-dihydroxy-6,6-dimethylbicyclo[3.1.1]hept-2-yl)methyl]-3-phenylthiourea (6).

Yield: 88%; m.p.: 147–149 ºC; [α]\textsuperscript{20}_D: +107 (0.25, EtOH); Anal. Calcd for C\textsubscript{24}H\textsubscript{30}N\textsubscript{2}O\textsubscript{2}S (410.57): C, 70.21; H, 7.36; N, 6.82%. Found: C, 70.46; H, 7.88; N, 6.53%. \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) (ppm): 0.93 (3H, s), 1.31 (3H, s), 1.46 (1H, \(d, J = 10.2\) Hz), 1.69 (1H, \(ddd, J = 2.4, 5.1, 14.1\) Hz), 1.94-1.98 (1H, \(m\)), 2.23-2.31 (1H, \(m\)), 2.46-2.52 (1H, \(m\)), 3.64 (1H, \(d, J = 15.4\) Hz), 4.03-4.11 (1H, \(m\)), 4.25 (1H, \(dd, J = 5.3, 9.2\) Hz), 4.90 (1H, \(br\ s\)), 5.15 (1H, \(d, J = 15.6\) Hz), 5.40 (1H, \(d, J = 15.4\) Hz), 7.15-7.18 (1H, \(m\)), 7.30-7.42 (9H, \(m\)), 9.30 (1H, \(br\ s\)). \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \(\delta\) (ppm): 24.1, 27.6, 27.9, 37.7, 38.7, 40.5, 51.0, 57.2, 66.0, 77.8, 124.8, 125.3, 126.9, 127.8, 128.5, 129.0, 140.2, 185.4.

1-Benzyl-1-[(2,3-dihydroxy-6,6-dimethylbicyclo[3.1.1]hept-2-yl)methyl]-3-(3’-methoxy-phenyl)thiourea (7).

Yield: 77%; m.p.: 149–151 ºC; [α]\textsuperscript{20}_D: +82 (0.25, EtOH); Anal. Calcd for C\textsubscript{25}H\textsubscript{32}N\textsubscript{2}O\textsubscript{3}S (440.60): C, 68.15; H, 7.32; N, 6.36%. Found: C, 68.43; H, 7.54; N, 6.11%; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) (ppm): 0.87 (3H, s), 1.30 (3H, s), 1.40 (1H, \(d, J = 9.7\) Hz), 1.66 (1H, \(ddd, J = 2.0, 4.8, 14.2\) Hz), 1.91-1.95 (1H, \(m\)), 2.23-2.29 (2H, \(m\)), 2.42-2.48 (1H, \(m\)), 3.46-3.54 (2H, \(m\)), 3.79 (1H, \(s\)), 3.89 (1H, \(br\ s\)), 4.10 (1H, \(br\ s\)), 5.06 (1H, \(br\ s\)), 5.44 (1H, \(br\ s\)), 6.70 (1H, \(dd, J = 2.2, 8.2\) Hz), 6.94 (1H, \(d, J = 7.4\) Hz), 7.10 (1H, \(s\)), 7.21 (1H, \(t, J = 8.1\) Hz), 7.28-7.34 (3H, \(m\)), 7.39 (2H, \(t, J = 7.6\) Hz), 9.80 (1H, \(br\ s\)). \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \(\delta\) (ppm): 24.0, 27.5, 27.8, 37.7, 38.6, 40.3, 50.2, 55.4, 57.1, 60.2, 65.6, 77.9, 110.4, 110.9, 116.9, 127.0, 127.7, 128.9, 129.2, 135.9, 141.4, 159.8, 185.0.

1-Benzyl-1-[(2,3-dihydroxy-6,6-dimethylbicyclo[3.1.1]hept-2-yl)methyl]-3-ethylthiourea (8).

Yield: 75%; an oil; [α]\textsuperscript{20}_D: +50 (0.28, EtOH); Anal. Calcd for C\textsubscript{20}H\textsubscript{30}N\textsubscript{2}O\textsubscript{2}S (362.53): C, 66.26; H, 8.34; N, 7.73%. Found: C, 66.51; H, 8.02; N, 7.96%; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \(\delta\) (ppm): 0.67 (3H, s), 0.92 (1H, \(t, J = 7.3\) Hz), 1.05 (3H, s), 1.19 (1H, \(d, J = 10.3\) Hz), 1.46 (1H, \(ddd, J = 2.3, 5.2, 14.2\) Hz), 1.68-1.72 (1H, \(m\)), 1.96 (1H, \(t, J = 5.9\) Hz), 1.99-2.04 (1H, \(m\)), 2.21-2.27 (1H, \(m\)), 3.21 (1H, \(d, J = 15.3\) Hz), 3.36-3.41 (2H, \(m\)), 3.80 (1H, \(br\ s\)), 3.98 (1H, \(dd, J = 5.0, 9.0\) Hz), 4.89 (1H, \(br\ s\)), 6.99 (1H, \(d, J = 7.6\) Hz), 7.04-7.07 (1H, \(m\)), 7.12 (1H, \(t, J = 7.5\) Hz). \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \(\delta\) (ppm): 14.3, 24.1, 27.6, 27.8, 37.8, 38.6, 40.4, 41.4, 50.6, 56.6, 60.3, 65.6, 77.6, 126.7, 127.6, 128.9, 135.8, 184.6.

1-[(2,3-Dihydroxy-6,6-dimethylbicyclo[3.1.1]hept-2-yl)methyl]-3-phenylthiourea (9).

Yield: 90%; m.p.: 110–113 ºC; [α]\textsuperscript{20}_D: -12 (0.25, EtOH); Anal. Calcd for C\textsubscript{17}H\textsubscript{24}N\textsubscript{2}O\textsubscript{2}S (320.45): C,
63.72; H, 7.55; N, 8.74%. Found: C, 64.11; H, 7.89; N, 8.36%. \( ^1 \)H NMR (CDCl\(_3\)) \( \delta \) (ppm): 1.04 (3H, s), 1.26 (3H, s), 1.37 (1H, \( d, J = 10.4 \) Hz), 1.63 (1H, \( ddd, J = 2.3, 4.6, 14.1 \) Hz), 1.89-1.93 (1H, \( m \)), 2.02-2.05 (1H, \( m \)), 2.18-2.23 (1H, \( m \)), 2.45-2.51 (1H, \( m \)), 3.46 (1H, \( br \) s), 3.60 (1H, \( br \) s), 3.99 (1H, \( br \) s), 4.12 (1H, \( br \) s), 4.20-4.27 (1H, \( m \)), 6.86 (1H, \( br \) s), 7.22-7.30 (3H, \( m \)), 7.36-7.41 (2H, \( m \)), 8.42 (1H, \( br \) s). \( ^{13} \)C NMR (CDCl\(_3\)) \( \delta \) (ppm): 24.1, 27.5, 27.6, 38.1, 38.8, 40.5, 50.3, 54.7, 65.8, 124.8, 127.0, 130.0, 136.2, 183.2.

1-[(2,3-Dihydroxy-6,6-dimethylbicyclo[3.1.1]hept-2-yl)methyl]-3-(3'-methoxyphenyl)thiourea (10). Yield: 87%; m.p.: 83–85 °C; \([\alpha]_{D}^{20}= -11\) (0.25, EtOH); Anal. Calcd for C\(_{18}\)H\(_{26}\)N\(_2\)O\(_2\)S (350.48): C, 61.69; H, 7.48; N, 7.99%. Found: C, 61.85; H, 7.23; N, 8.12%; \( ^1 \)H NMR (CDCl\(_3\)) \( \delta \) (ppm): 1.05 (3H, s), 1.27 (3H, s), 1.39 (1H, \( d, J = 10.4 \) Hz), 1.62-1.67 (1H, \( m \)), 1.90-1.94 (1H, \( m \)), 2.05 (1H, \( t, J = 5.7 \) Hz), 2.18-2.24 (1H, \( m \)), 2.49 (1H, \( t, J = 11.2 \) Hz), 3.28 (1H, \( br \) s), 3.62 (1H, \( dd, J = 3.8, 13.5 \) Hz), 3.79 (3H, \( s \)), 3.98 (1H, \( br \) s), 4.23-4.28 (1H, \( m \)), 6.79 (1H, \( d, J = 8.3 \) Hz), 6.83-6.87 (2H, \( m \)), 6.96 (2H, \( br \) s), 7.26-7.30 (1H, \( m \)), 8.26 (2H, \( br \) s). \( ^{13} \)C NMR (CDCl\(_3\)) \( \delta \) (ppm): 24.0, 27.5, 27.6, 38.1, 38.9, 40.6, 50.5, 54.8, 55.4, 65.9, 76.0, 110.1, 112.8, 116.5, 130.7, 160.8, 180.8.

1-[(2,3-Dihydroxy-6,6-dimethylbicyclo[3.1.1]hept-2-yl)methyl]-3-ethylthiourea (11). Yield: 85%; m.p.: 140–142 °C; \([\alpha]_{D}^{20}= -8\) (0.25, EtOH); Anal. Calcd for C\(_{19}\)H\(_{28}\)N\(_2\)O\(_2\)S (272.41): C, 57.32; H, 8.88; N, 10.28%. Found: C, 57.55; H, 8.63; N, 10.51%; \( ^1 \)H NMR (CDCl\(_3\)) \( \delta \) (ppm): 1.02 (3H, s), 1.23 (1H, \( t, J = 7.2 \) Hz), 1.29 (3H, \( s \)), 1.42 (1H, \( d, J = 10.6 \) Hz), 1.68 (1H, \( ddd, J = 2.2, 4.8, 14.1 \) Hz), 1.92-1.96 (1H, \( m \)), 2.08 (1H, \( t, J = 5.7 \) Hz), 2.22-2.27 (1H, \( m \)), 2.47-2.53 (1H, \( m \)), 3.44-3.52 (3H, \( m \)), 4.26 (1H, \( dd, J = 5.1, 9.4 \) Hz), 6.80-6.94 (2H, \( m \)). \( ^{13} \)C NMR (CDCl\(_3\)) \( \delta \) (ppm): 14.2, 24.1, 27.5, 27.6, 37.7, 37.8, 38.8, 40.6, 50.5, 54.5, 65.7, 76.4, 182.6.

**General procedure for the preparation of spiro-2-iminoaxazolidine derivatives 12-17**

Iodomethane (0.53 g, 3.70 mmol) was added dropwise to a solution of the appropriate thiourea adduct 6-11 (0.70 mmol) in dry methanol (10 mL). After stirring for 6 h at room temperature, the solvent was removed under reduced pressure, after which a methanolic solution of KOH (2.5 M, 10 mL) was added to the residue. The resulting solution was then stirred for 4 h, followed by evaporation to dryness. Water (30 mL) was added to this residue and the resulting suspension was extracted with CHCl\(_3\) (3 × 40 mL). The organic layer was dried over Na\(_2\)SO\(_4\), filtered and then evaporated to dryness, yielding in a crystalline product, which was purified by flash chromatography over silica gel with an EtOAc:n-hexane = 1:1 mixture.

**3'-Benzy1-6,6-dimethyl-2'-(phenylimino)spiro[bicyclo[3.1.1]heptane-2,5'-oxazolidin]-3-ol (12).** Yield: 64%; m.p.: 140–141 °C; \([\alpha]_{D}^{20}= +3\) (0.25, EtOH); Anal. Calcd for C\(_{24}\)H\(_{28}\)N\(_2\)O\(_2\) (376.49): C, 76.56; H, 7.50; N, 7.44%. Found: C, 76.98; H, 7.54; N, 7.00%; \( ^1 \)H NMR (CDCl\(_3\)) \( \delta \) (ppm): 0.79 (3H, s), 1.25 (3H, s), 1.47 (1H, \( d, J = 10.4 \) Hz), 1.69-1.77 (1H, \( m \)), 1.94-2.01 (1H, \( m \)), 2.22-2.33 (2H, \( m \)), 2.37-2.47 (1H, \( m \)), 3.18 (1H, \( d, J = 8.7 \) Hz), 3.34 (1H, \( d, J = 8.7 \) Hz), 4.11 (1H, \( dd, J = 4.9, 8.3 \) Hz), 4.52 (1H, \( d, J = 15.1 \) Hz), 4.66 (1H, \( d, J = 15.1 \) Hz), 6.96 (1H, \( t, J = 7.2 \) Hz), 7.10-7.38 (9H, \( m \)). \( ^{13} \)C NMR (CDCl\(_3\)) \( \delta \) (ppm): 23.1, 27.1, 27.7, 37.3, 38.8, 40.2, 48.9, 51.2, 56.9, 69.5, 86.2, 122.0, 123.5, 127.6, 128.0, 128.5, 128.7, 136.5, 151.5.
3'-Benzy1-6, 6-dimethyl-2'-[(3-methoxyphenyl)imino]spiro[bicyclo[3.1.1]heptane-2, 5'- oxazolidin]-3-ol (13). Yield: 88%; m.p.: 116–118 ºC; [α]D 20: +36 (0.25, EtOH); Anal. Calcd for C25H30N2O3 (406.52): C, 73.86; H, 7.44; N, 6.89%. Found: C, 73.97; H, 7.31; N, 6.99%; 1H NMR (CDCl3) δ (ppm): 0.63 (3H, s), 1.08 (3H, s), 1.32 (1H, d, J = 10.5 Hz), 1.53-1.59 (1H, m), 1.79-1.82 (1H, m), 2.09 (1H, t, J = 5.8 Hz), 2.11-2.15 (1H, m), 2.22-2.30 (2H, m), 3.01 (1H, d, J = 8.7 Hz), 3.15 (1H, d, J = 8.7 Hz), 3.60 (3H, s), 3.90-3.95 (1H, m), 4.35 (1H, d, J = 15.4 Hz), 4.42 (1H, d, J = 15.4 Hz), 6.37 (1H, dd, J = 2.1, 8.3 Hz), 6.52-6.55 (2H, m), 6.96 (1H, t, J = 8.1 Hz), 7.10-7.20 (5H, m). 13C NMR (CDCl3) δ (ppm): 23.1, 27.2, 27.8, 37.5, 38.8, 40.3, 48.9, 51.3, 55.2, 56.8, 69.5, 85.9, 108.1, 109.0, 116.1, 127.6, 128.0, 128.7, 129.1, 136.7, 149.0, 151.4, 160.0.

3'-Benzy1-2'-(ethylimino)-6, 6-dimethylspiro[bicyclo[3.1.1]heptane-2, 5'- oxazolidin]-3-ol (14). Yield: 66%; an oil; [α]D 20: +2 (0.30, EtOH); Anal. Calcd for C20H28N2O2 (328.45): C, 73.14; H, 8.59; N, 8.53%. Found: C, 73.42; H, 8.65; N, 8.21%; 1H NMR (CDCl3) δ (ppm): 0.77 (3H, s), 1.15 (1H, d, J = 7.2 Hz), 1.24 (3H, s), 1.56 (1H, d, J = 10.7 Hz), 1.80 (1H, dd, J = 3.0, 4.4, 14.2 Hz), 1.96-2.00 (1H, m), 2.19 (1H, t, J = 5.6 Hz), 2.25-2.30 (1H, m), 2.39-2.44 (1H, m), 3.10 (1H, d, J = 8.6 Hz), 3.21 (1H, d, J = 8.6 Hz), 3.30 (2H, q, J = 7.0 Hz), 4.07 (1H, dd, J = 4.6, 8.9 Hz), 4.35 (1H, d, J = 15.1 Hz), 4.42 (1H, d, J = 15.1 Hz), 7.24-7.27 (3H, m), 7.30-7.33 (2H, m). 13C NMR (CDCl3) δ (ppm): 17.1, 23.1, 27.2, 27.4, 37.3, 38.9, 40.2, 41.0, 49.0, 51.0, 57.5, 59.1, 84.5, 127.3, 127.9, 128.6, 137.1, 152.4.

6,6-Dimethyl-2'-(phenylimino)spiro[bicyclo[3.1.1]heptane-2, 5'-oxazolidin]-3-ol (15). This compound was purified as a hydrochloride salt. Yield: 65%; m.p.: 175–178 ºC; [α]D 20: -1.0 (0.25, EtOH); Anal. Calcd for C17H23ClN2O2 (322.83): C, 73.25; H, 7.18; N 8.68%. Found: C, 63.37; H, 7.28; N, 8.29%; 1H NMR (DMSO-d6) δ (ppm): 0.88 (3H, s), 1.24 (3H, s), 1.47 (1H, d, J = 9.9 Hz), 1.66 (1H, dd, J = 2.9, 4.8, 13.9 Hz), 1.89-1.96 (1H, m), 2.10 (1H, t, J = 5.5 Hz), 2.19-2.27 (1H, m), 2.29-2.38 (1H, m), 3.57 (1H, d, J = 12.1 Hz), 3.66 (1H, d, J = 12.1 Hz), 4.04-4.12 (1H, m), 4.87 (1H, d, J = 5.5 Hz), 6.84 (1H, d, J = 7.3 Hz), 7.18 (2H, J = 7.8 Hz), 7.46-7.60 (2H, m), 8.90 (1H, br s). 13C NMR (CDCl3) δ (ppm): 23.1, 27.0, 27.9, 37.2, 38.1, 39.2, 39.8, 51.4, 69.4, 88.0, 117.5, 120.4, 128.3, 155.0, 171.0.

6,6-Dimethyl-2'-(3-methoxyphenyl)imino]spiro[bicyclo[3.1.1]heptane-2, 5'-oxazolidin]-3-ol (16). Yield: 90%; m.p.: 143–145 ºC; [α]D 20: +11 (0.25, EtOH); Anal. Calcd for C17H22N2O2 (286.37): C, 71.30; H, 7.74; N, 9.78%. Found: C, 71.45; H, 7.54; N, 9.93%; 1H NMR (CDCl3) δ (ppm): 0.89 (3H, s), 1.31 (3H, s), 1.55 (1H, d, J = 8.8 Hz), 1.80-1.84 (1H, m), 1.99-2.03 (1H, m), 1.99-2.03 (1H, m), 2.28-2.33 (2H, m), 2.43-2.49 (1H, m), 3.63-3.79 (5H, m), 4.18 (1H, dd, J = 4.6, 8.8 Hz), 6.55 (1H, dd, J = 1.8, 8.3 Hz), 6.84 (1H, br s), 7.00 (1H, br s), 7.15 (1H, t, J = 8.3 Hz). 13C NMR (CDCl3) δ (ppm): 23.2, 27.1, 28.0, 37.3, 38.8, 39.5, 40.4, 51.5, 55.2, 70.4, 89.9, 108.2, 129.6, 141.3, 160.2, 160.4.

2'-(Ethylimino)-6,6-dimethylspiro[bicyclo[3.1.1]heptane-2, 5'-oxazolidin]-3-ol (17). Yield: 77%; m.p.: 131–133 ºC; [α]D 20: +5 (0.25, EtOH); Anal. Calcd for C13H22N2O2 (238.33): C, 65.51; H, 9.30; N, 11.75%. Found: C, 65.75; H, 9.21; N, 11.83%; 1H NMR (CDCl3) δ (ppm): 0.84 (3H, s), 1.13 (3H, t, J = 7.2 Hz), 1.24 (3H, s), 1.45 (1H, d, J = 10.2 Hz), 1.74-1.79 (1H, m), 1.93-1.96 (1H, m), 2.18 (3H, t, J = 5.4 Hz), 2.20-2.25 (1H, m), 2.36-2.42 (1H, m), 3.18 (1H, d, J
= 7.0 Hz), 3.20 (1H, d, J = 7.0 Hz), 3.58 (1H, d, J = 12.3 Hz), 3.64 (1H, d, J = 7.0 Hz), 4.10 (1H, dd, J = 4.2, 8.8 Hz). $^{13}$C NMR (CDCl$_3$) δ (ppm): 15.1, 23.2, 27.1, 27.7, 37.2, 37.6, 38.8, 40.3, 51.6, 66.3, 70.5, 90.2, 158.8.

6,6-Dimethyl-2'-((4-chlorophenyl)-4'H-spiro[bicyclo[3.1.1]heptane-2,5'-oxazol]-3-ol (20)

Ethyl 4-chlorobenzimidate (0.18 g, 1 mmol) and 1 drop of glacial acetic acid were added to a solution of aminodiol 5 (0.19 g, 1 mmol) in 15 mL of dry ethanol. The solution was refluxed for 8 h, and then evaporated, and the crude product was purified by flash chromatography over silica gel with an EtOAc:n-hexane = 2:1 mixture ($R_f = 0.24$). Yield: 0.17 g (55%); m.p.: 146–147 ºC; \([\alpha]^D_{20} = -2\) (0.25, EtOH); Anal. Calcd for C$_{17}$H$_{20}$ClNO$_2$ (305.80): C, 66.77; H, 6.59; N, 4.58%. Found: C, 66.83; H, 6.87; N, 4.90%; $^1$H NMR (CDCl$_3$) δ (ppm): 0.94 (3H, s), 1.31 (3H, s), 1.64 (1H, d, J = 10.5 Hz), 1.87 (1H, dt, J = 3.6, 14.3 Hz), 2.02-2.08 (1H, m), 2.24 (1H, t, J = 5.6 Hz), 2.30-2.38 (1H, m), 2.46-2.54 (2H, m), 3.75 (1H, d, J = 15.1 Hz), 3.84 (1H, d, J = 15.1 Hz), 4.15-4.21 (1H, m), 7.39 (2H, d, J = 8.5 Hz), 7.87 (2H, d, J = 8.5 Hz). $^{13}$C NMR (CDCl$_3$) δ (ppm): 23.6, 27.4, 28.5, 37.9, 38.6, 40.4, 52.4, 68.3, 70.8, 90.6, 127.5, 129.0, 130.2, 136.3, 161.3.

3,3-Dimethyl-2,4-methylene-7,11-dioxa-9-atracyclo[7.2.1.0$^{1,6}$]dodecane (21)

Aminodiol 5 was stirred with 10 mL of 33% aqueous formaldehyde for 4 h at room temperature. Water (30 mL) was next added to the reaction mixture and the solution was extracted with CHCl$_3$ (3 × 40 mL). The organic layer was dried over Na$_2$SO$_4$, filtered and then evaporated to dryness, furnishing in a colorless oil, which was purified by flash chromatography over silica gel with a toluene:EtOH = 9:1 mixture ($R_f = 0.35$). Yield: 60%; a colorless oil; [\(\alpha\)]$^D_{20}$ = +7 (0.30, EtOH); Anal. Calcd for C$_{12}$H$_{19}$NO$_2$ (209.28): C, 68.87; H, 9.15; N, 6.69%. Found: C, 69.09; H, 9.31; N, 6.78%; $^1$H NMR (CDCl$_3$) δ (ppm): 1.07 (3H, s), 1.29 (3H, s), 1.71 (1H, dd, J = 9.8, 13.2 Hz), 1.77 (1H, d, J = 10.0 Hz), 1.97 (1H, q, J = 5.9 Hz), 2.04 (1H, t, J = 5.8 Hz), 2.14-2.17 (1H, m), 2.33-2.35 (1H, m), 2.79 (1H, d, J = 11.2 Hz), 3.26 (1H, d, J = 11.2 Hz), 4.17 (1H, t, J = 9.0 Hz), 4.37 (1H, dd, J = 1.5, 5.3 Hz), 4.41 (1H, dd, J = 1.4, 9.8 Hz), 4.51 (1H, dd, J = 1.1, 9.8 Hz), 4.70 (1H, d, J = 5.3 Hz). $^{13}$C NMR (CDCl$_3$) δ (ppm): 24.5, 29.1, 31.9, 32.0, 39.0, 41.8, 48.8, 62.7, 77.5, 81.0, 83.3, 87.3.

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