Supporting Information

for

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

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Experimental

$^1$H and $^{13}$C NMR spectra were recorded on Bruker Avance DRX 400 or Bruker Avance DRX 500 spectrometer [$\delta = 0$ (TMS)] (Bruker Corp., Billerica, MA, USA) in solvents as indicated. Chemical shifts are expressed in ppm ($\delta$) 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 a 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). 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. (1R)−(−)−Myrtenol (10) (ee > 95%) and (1S,5S)−(−)(α)−pinene (ee > 95%) were obtained from Merck Hungary Co. Isopinocarveol (7) was prepared from commercially available (1S,5S)−(−)(α)−pinene (6) using a literature method [1], with all spectroscopic data and physical properties similar to those reported therein.

General procedure for carbamate formation

Trichloroacetyl isocyanate (6.78 g, 35.99 mmol) was added dropwise to a solution of the allylic alcohol (4.50 g, 29.56 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). An aqueous solution of K$_2$CO$_3$ (4.30 g in 15 mL of H$_2$O) was added to the solution at 0 °C and the mixture was allowed to stir for 4 h (TLC monitoring). The MeOH was evaporated under reduced pressure and the aqueous residue was extracted with DCM (3 × 50 mL). The combined organic phase was dried (Na$_2$SO$_4$), 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).

**(1R,3S,5R)-6,6-Dimethyl-2-methylenebicycle[3.1.1]heptan-3-yl carbamate (8)**

Compound 8: synthesis was performed starting from (−)-isopinocarveol, 4.18 g (72%), white crystalline powder, mp: 113–115 °C, [$\alpha$]$_{D}^{20}$ = +12.5 (c = 0.315, MeOH). $^1$H NMR (500.2 MHz, CDCl$_3$): $\delta$ = 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$_3$): $\delta$ = 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$_2$: C, 67.66; H, 8.78; N, 7.17; Found: C, 67.42; H, 8.80; N, 7.52. HRMS-ESI [M+H]+/m/z found 196.13276, calcd for C$_{11}$H$_{18}$NO$_2$: 196.13375.
[(1R,5S)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl]methyl carbamate (11)

Compound 11: synthesis was performed starting from (1R)-(−)-myrtenol, 4.65 g (80%), white crystals, all physical and chemical properties are similar to those reported in the literature, [2] [α]D20 = −43 (c = 0.265, MeOH), Anal. calcd for C11H17NO2 (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 found 196.13289, calcd for C11H18NO2: 196.13375.

General method for the aminohydroxylation process

To a solution of allylic carbamate 8 or 11 (2.00 g, 10.24 mmol) in iPrOH (180 mL), freshly prepared 0.33% aqueous solution of NaOH (80 mL) was added. The solution was allowed to stir for 5 min, then t-BuOCl (1.026 mL, 10.30 mmol) was added. After stirring for 5 min, N,N-diisopropylethylamine (59 mg, 79.5 μL, 0.46 mmol) and potassium osmate(VI) dihydrate (135 mg, 0.366 mmol) were added to the solution in one portion. After the addition of 0.33% aqueous NaOH solution (20 mL), the mixture was stirred for 24 h (TLC monitoring), then quenched with Na2SO3 (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 (Na2SO4), 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).

(3aS,4R,6R,7aS)-3a-Hydroxymethyl-5,5-dimethylhexahydro-4,6-methanobenzo[d]oxazol-2(3H)-one (9)

Compound 9: 0.86 g (40%), white crystalline powder, mp: 195–197 °C, [α]D20 = +31 (c = 0.290, MeOH), 1H NMR (400 MHz, DMSO-d6): 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 = 5.0 Hz), 5.07 (d, 1H, J = 5.0 Hz), 7.69 (br s, 1H), 13C NMR (100 MHz, DMSO-d6): 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 C11H18NO3 (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 found 212.12775, calcd for C11H18NO3: 212.12867.

(1R,2S,3S,5R)-3-hydroxy-6,6-dimethylspiro[bicyclo[3.1.1]heptane-2,4'-oxazolidin]-2'-one (12)

Compound 12: 1.08 g (50%), white crystalline powder, mp: 153–156 °C, [α]D20 = −55 (c = 0.285, MeOH), 1H NMR (400 MHz, DMSO-d6): 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), 13C NMR (100 MHz, DMSO-d6): δ = 24.3, 26.7, 27.3, 34.8, 38.5, 39.4, 65.7, 65.8, 71.4, 158.1. Anal. calcd for C11H17NO3 (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 found 212.12775, calcd for C11H18NO3: 212.12867.
General method for the alkaline hydrolysis of oxazolidinones

To a solution of oxazolidinone 9 or 12 (1.70 g, 8.05 mmol) in dry EtOH (21 mL), 14% aqueous solution of NaOH (10 mL) was added and the mixture was heated under reflux 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 (Na$_2$SO$_4$), filtered and concentrated under reduced pressure to yield crude product 13, which was purified as a hydrochloride salt by recrystallization from an EtOH/Et$_2$O mixture.

\[(1R,2S,3S,5R)-2\text{-Amino-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-3-ol hydrochloride (13)}\]

Compound 13: 0.91 g (51%) from 9 and 0.80 g (45%) from 12, white crystalline powder, mp: 195–196 °C, $[\alpha]_D^{20} = +7$ (c = 0.270, MeOH), $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta = 0.92$ (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$_6$): $\delta = 24.3, 27.1, 27.7, 37.7, 39.2, 40.4, 45.9, 63.3, 64.9$. Anal. calcd for C$_{10}$H$_{20}$ClNO$_2$: 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 found 186.14915, calcd for C$_{10}$H$_{20}$NO$_2$: 186.14940.

General method for the LAH reduction of oxazolidinones 9 and 12

To the stirred suspension of LiAlH$_4$ (0.25 g, 6.59 mmol) in dry THF (5 mL) the solution of 9 or 12 (0.35 g, 1.656 mmol) in dry THF (5 mL) was added dropwise under ice cooling. The reaction mixture was treated under reflux conditions for 2 h, then a mixture of H$_2$O (0.50 mL) and THF (5 mL) was added dropwise with cooling. After 30 min of stirring, the inorganic material was filtered off and washed with THF (3 × 30 mL). The filtrate was dried (Na$_2$SO$_4$), filtered and evaporated. The obtained crude product was purified by column chromatography on silica gel (toluene/EtOH 1:1).

\[(1R,2S,3S,5R)-2\text{-Hydroxymethyl-6,6-dimethyl-2-methylaminobicyclo[3.1.1]heptan-3-ol (14)}\]

Compound 12: 0.20 g (60%) from 9 and 0.18 g (55%) from 12, white crystalline powder, mp: 126–128 °C, $[\alpha]_D^{20} = -3$ (c = 0.200, MeOH), $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta = 0.91$ (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, DMSO-d$_6$): $\delta = 24.9, 27.6, 28.1, 28.8, 38.4, 38.8, 40.4, 46.6, 61.5, 64.8, 66.8$. Anal. calcd for C$_{11}$H$_{22}$ClNO$_2$: 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 found 200.16391, calcd for C$_{11}$H$_{22}$NO$_2$: 200.16451.
Preparation of the 15A–E tautomeric mixture

Aminodiol 13 (20.0 mg, 0.11 mmol) and benzaldehyde (10.2 µL, 10.6 mg, 0.11 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 15A–E that was examined in CDCl3.

Compounds 15A–E: 0.030 g (98%) crude mixture. Ratio of 15A:15B:15C:15D:15E: 4:1:4:1:2.79 based on 1H NMR and 2D NMR (NOESY and HMBC) measurement. Characteristic chemical shifts for the C-2 methyne peaks of tautomers: 1H NMR (500.2 MHz, CDCl3): δ = 8.02 (d, J = 6.5 Hz): 15A, 5.90 (s): 15B/15C, 5.41 (s): 15D, 5.30 (s): 15E.

(1R,2S,3S,5R)-2-Benzylamino-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-3-ol (16)

To a solution of aminodiol 14 (liberated base, 0.60 g, 3.24 mmol) in dry ethanol (20 mL) benzaldehyde (0.343 g, 0.328 mL, 3.24 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 LiAlH4 (0.491 g, 12.95 mmol). The reaction mixture was treated under reflux conditions for 3 h, then a mixture of H2O (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 (Na2SO4), filtered and evaporated. The obtained crude product was purified by column chromatography on silica gel (CHCl3/MeOH 9:1).

Compound 16: 0.66 g (75%), white crystalline powder, mp: 112–114 °C, [a]D20 = +10.8 (c = 0.320, MeOH), 1H NMR (400 MHz, DMSO-d6): 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 H2O 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, 2H), 7.18-7.37 (m, 5H), 13C NMR (400 MHz, DMSO-d6): 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 C17H25NO2 (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 found 276.19634, calcd for C17H26NO2: 276.19635.

((3aS,4R,6R,7aS)-3-Benzyl-5,5-dimethyloctahydro-4,6-methanobenzol[d]oxazol-3-yl)methanol (17)

In a manner similar to a procedure in [3], to the solution of 16 (0.25 g, 0.91 mmol) in Et2O (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 Et2O (3 × 30 mL). The combined organic layer was washed with saturated NaCl solution (2 × 20 mL) then dried (Na2SO4), filtered and evaporated to dryness. The crude product was purified by column chromatography on silica gel (n-hexane/EtOAc 3:2).

Compound 17: 0.23 g (89%), pale-yellow crystalline powder, mp: 77–78 °C, [a]D20 = +3 (c = 0.285, MeOH), 1H NMR (400 MHz, CDCl3): 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), 3.13 (br s, 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$_3$): $\delta$ = 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$_{25}$N$_2$O$_2$ (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 found 288.19544, calcd for C$_{18}$H$_{26}$N$_2$O$_2$: 288.19581.

(1R,2S,3S,5R)-2-(N-Benzyl-N-methy lamino)-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-3-ol (18)

To the stirred suspension of LiAlH$_4$ (0.166 g, 4.38 mmol) in dry THF (5 mL) the solution of 17 or 19 (1.46 mmol) in dry THF (5 mL) was added dropwise at room temperature. After a 12 h treatment under reflux conditions a mixture of H$_2$O (0.30 mL) and THF (4 mL) was added dropwise with cooling to the reaction mixture. After 30 min of stirring, the inorganic material was filtered off and washed with THF (3 × 20 mL). The filtrate was dried (Na$_2$SO$_4$), filtered, and evaporated. The obtained crude product was purified by column chromatography on silica gel (DCM/MeOH 19:1).

Compound 18: 0.26 g (60%) from 17, 0.32 g (74%) from 19, colourless oil, [α]$_D^{20}$ = −40 (c = 0.365, MeOH), $^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ = 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), 3.65-3.72 (m, 2H), 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$_3$): $\delta$ = 23.9, 26.3, 28.2, 37.1, 38.5, 38.8, 39.5, 45.1, 57.3, 62.7, 64.1, 64.7, 128.3, 128.8, 129.9, 135.7. Anal. calcd for C$_{18}$H$_{27}$N$_2$O$_2$ (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 found 290.21080, calcd for C$_{18}$H$_{28}$N$_2$O$_2$: 290.21146.

(3aS,4R,6R,7aS)-3-Benzyl-3a-(hydroxymethyl)-5,5-dimethylhexahydro-4,6-methanobenzo[d]oxazol-2(3H)-one (19)

To a solution of 9 (0.30 g, 1.42 mmol) in DMF (10 mL), benzyl bromide (0.291 g, 0.202 mL, 1.7 mmol), Cs$_2$CO$_3$ (0.300 g, 0.92 mmol), and a catalytic amount of KI (16.0 mg) were added and the mixture was stirred for 24 h at 80 °C. After cooling and removal of the solid by filtration, the solvent was evaporated under vacuum and the residual oily product was dissolved in a mixture of DCM (20 mL) and H$_2$O (20 mL). The aqueous phase was extracted with DCM (3 × 20 mL) and the combined organic layer was dried (Na$_2$SO$_4$), filtered, and evaporated to dryness. The crude product was purified by column chromatography on silica gel (DCM/MeOH 19:1).

Compound 19: 0.19 g (45%), yellow oil, [α]$_D^{20}$ = −20 (c = 0.285, MeOH), $^{1}$H NMR (400 MHz, CDCl$_3$): $\delta$ = 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), 3.40 (dd, 1H, J = 5.7, 12.1 Hz), 3.47 (dd, 1H, J = 5.6, 12.2 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$_3$): $\delta$ = 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 found 302. 17511, calcd for C_{18}H_{24}NO_{3}: 302.17562.

1-((1R,2S,3S,5R)-3-Hydroxy-2-hydroxymethyl-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)-3-phenylthiourea (20)

To a solution of aminodiol 13 (84 mg, 0.377 mmol) in toluene (30 mL), 1.05 equiv of phenyl isothiocyanate (54 mg, 47 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 (CHCl₃/MeOH 19:1).

Compound 20: 85 mg (70%), white powder, mp: 168–170 °C, [α]_{D}^{20} = +134 (c = 0.275, MeOH), ¹H NMR (500 MHz, CDCl₃) 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), 1.91-1.94 (m, 1H), 2.15-2.32 (m, 1H), 2.39-2.43 (m, 1H), 2.65 (s, 1H), 3.27 (t, 1H, J = 5.8 Hz), 3.68 (d, 1H, J = 11.1 Hz), 4.56 (t, 1H, J = 8.2 Hz), 4.92 (d, 1H, J = 10.9 Hz), 7.23-7.29 (m, 2H), 7.40-7.43 (m, 3H), 7.60 (s, 1H); ¹³C NMR (125 MHz, CDCl₃) 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_{2}O_{3}: 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 found 321.16303, calcd for C_{17}H_{25}N_{2}O_{2}S: 321.16367.

(1R,2S,3S,5R)-6,6-Dimethyl-2'-{(phenylimino)spiro[bicyclo[3.1.1]heptan-2,4'-oxazolidine]-3-ol (21A)

Thiourea 20 (56 mg, 0.174 mmol) was dissolved and stirred in a solution of methanol (5 mL) and MeI (5.5 equiv, 60 µL, 0.96 mmol) at room temperature. After stirring for 3 h 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 a mixture of H₂O (10 mL) and CHCl₃ (10 mL) and the aqueous phase was extracted with CHCl₃ (2 × 10 mL) and the organic layer was dried (Na₂SO₄), and evaporated. The crude product was then purified by column chromatography on silica gel (n-hexane/EtOAc 1:1).

Compound 21A: 33 mg (66%), orange solid, mp: 138–140 °C, [α]_{D}^{20} = +13 (c = 0.335, MeOH), ¹H NMR (500 MHz, CDCl₃) δ = 0.85 (s, 3 H), 1.15-1.29 (m, 1H), 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, 3H), 7.40-7.41 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) 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, 139.1, 157.0. Anal. calcd for C_{17}H_{23}N_{2}O_{2} (286.37): 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 found 287.17545, calcd for C_{17}H_{23}N_{2}O_{2}: 287.17595.
(3aS,4R,6R,7aS)-5,5-dimethyl-2-(phenylimino)octahydro-4,6-methanobenzo[\(d\)]oxazol-3a-yl)methanol (21B)

From the CHCl\(_3\) solution of 21A (50 mg) standing for 30 days, both 21A and 21B tautomeric products were isolated by column chromatography on silica gel (CHCl\(_3\)/MeOH 19:1).

Compound 21B: 25 mg (50%), white solid, mp: 92–95 °C, \([\alpha]_D^{20} = +18\) (c = 0.200, MeOH). ¹H NMR (400 MHz, CDCl\(_3\)) \(\delta = 0.88\) (s, 3H), 1.20 (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), 3.60 (d, 1H, \(J = 11.1\) Hz), 3.66 (d, 1H, \(J = 11.1\) Hz), 4.80 (d, 1H, \(J = 8.1\) Hz), 7.03 (t, 1H, \(J = 7.1\) Hz), 7.27-7.30 (t, 3H, \(J = 7.8\) Hz), 7.37-7.38 (m, 2H), 13C NMR (125 MHz, CDCl\(_3\)) \(\delta = 24.5, 27.1, 27.3, 30.0, 34.5, 38.7, 39.3, 47.7, 68.0, 75.4, 119.14, 123.3, 129.4, 139.0, 156.6.\) Anal. calcd for C\(_{17}\)H\(_{22}\)N\(_2\)O\(_2\) (286.37): C, 71.30; H, 7.74; N, 9.78; Found: C, 71.11; H, 7.67; N, 9.93. HRMS-ESI \([M+H]^+ m/z\) found 287.17533, calcd for C\(_{17}\)H\(_{23}\)N\(_2\)O\(_2\): 287.17595.

X-Ray structure determinations

The crystals of 9 and 17 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 [4] software package was used for cell refinements and data reductions. A multi-scan (9) or an analytical absorption correction (17) was applied to the intensities before structure solutions by using CrysAlisPro [4] software. The structures were solved by intrinsic phasing (SHELXT [5]) method. Structural refinements were carried out using SHELXL [6] software with SHELXE [7] 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 summarized in Table S1.

The deposition number CCDC 2063842 (9) and CCDC 2063843 (17) contain supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk)
|                  | 9               | 17              |
|------------------|-----------------|-----------------|
| empirical formula | C₁₁H₁₇NO₃      | C₁₈H₂₅NO₂      |
| fw               | 211.25          | 287.39          |
| temp (K)         | 120(2)          | 120(2)          |
| λ(Å)             | 1.54184 Å       | 1.54184 Å       |
| cryst syst       | Monoclinic      | Monoclinic      |
| space group      | P₂₁            | P₂₁            |
| a (Å)            | 7.93530(6)      | a = 8.41050(10) |
| b (Å)            | 10.89885(6)     | b = 7.23460(10) |
| c (Å)            | 12.63719(8)     | c = 13.4036(2)  |
| β (deg)          | 97.9249(7)      | β = 102.960(2)° |
| V(Å³)            | 1082.498(12)    | 794.79(2)       |
| Z                | 4               | 2               |
| ρcalc (Mg/m³)    | 1.296           | 1.201           |
| μ(Mo Kα) (mm⁻¹) | 0.770           | 0.608           |
| No. reflns.      | 24009           | 16590           |
| Unique reflns.   | 4528            | 3329            |
| GOOF (F²)        | 1.042           | 1.038           |
| Rint             | 0.0194          | 0.0310          |
| R1² (I ≥ 2σ)     | 0.0249          | 0.0305          |
| wR2² (I ≥ 2σ)    | 0.0664          | 0.0766          |

*R1 = Σ||Fo| – |Fc||/Σ|Fo|.*  
*wR2 = [Σ[w(Fo² – Fc²)²]/Σ[w(Fo²)]²]¹/².

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$^1$H, $^{13}$C NMR, COSY, HSQC and HMBC of 8 (CDCl$_3$)
$^{1}H$, $^{13}C$ NMR, COSY, NOESY, HSQC and HMBC of 9 (DMSO-$d_6$)
$^{1}H$, $^{13}C$ NMR, COSY, NOESY, HSQC and HMBC of 12 (DMSO-$d_6$)
$^1\text{H}, \quad ^{13}\text{C} \quad \text{NMR}, \quad \text{COSY, NOESY, HSQC and HMBC of 13 (DMSO-}d_6\text{)}$
$^{1}\text{H}, ^{13}\text{C}$ NMR, COSY, HSQC and HMBC of 14 (DMSO-$d_6$)
$^1$H, $^{13}$C NMR, COSY, HSQC and HMBC of 16 (DMSO-$d_6$)
$^1$H, $^{13}$C NMR and HMBC of 17 (CDCl$_3$)
$^1$H, $^{13}$C NMR, COSY, HSQC and HMBC of 18 (CDCl$_3$)
$^1\text{H}, \ 13\text{C} \text{NMR, COSY, NOESY, HSQC and HMBC of 19 (DMSO-d}_6\text{)}$
$^1$H, $^{13}$C NMR, COSY, HSQC and HMBC of 20 (CDCl$_3$)
$^1\text{H}$, $^{13}\text{C}$ NMR, COSY, NOESY, HSQC and HMBC of 21A (CDCl$_3$)
$^1$H, $^{13}$C NMR, COSY, NOESY, HSQC and HMBC of 15A-E (CDCl$_3$)
$^1$H, $^{13}$C NMR, HSQC, HMBC, COSY and NOESY of 21B (CDCl$_3$)
Time-dependent tautomerisation of 21A to 21B in CDCl₃ solution