A New Synthesis of Optically Active 5-Isoxazolidinones and β -Amino Acids

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Experimental Section

General. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were freshly distilled under a nitrogen atmosphere over sodium/benzophenone ketyl. *N,N,N',N'*-Tetramethylethylenediamine (TMEDA) was distilled over finely powdered calcium hydride. The needed chiral 2-ethyl-2-oxazolines for the preparation of (+)-**9** and (+)/(-)**11** were prepared accordingly to a reported procedure starting from the corresponding commercially available aminoalcohols.¹ Nitrones **4a–e** were prepared accordingly to reported procedures.² Spectroscopic data of compounds **5a** and **6a** have been reported.³ All other chemicals were of commercial grade and used without further purification. Petroleum ether refers to the 40–60 °C boiling fraction. Commercial solutions of *n*-BuLi (2.5 M solution in hexanes) and *s*-BuLi (1.3 M solution in cyclohexane) were titrated by using *N*-pivaloyl-*o*-toluidine prior to use.⁴ For the ¹H and ¹³C NMR spectra (¹H NMR 300, 500 MHz; ¹³C NMR 75.4, 125 MHz), CDCl₃ or CD₃OD were used as the solvents. GC-MS spectrometry analyses were performed on a gas chromatograph HP 6890 plus (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.) equipped with a 5973 mass selective detector operating at 70 eV (EI). MS – ESI analyses were performed on Agilent 1100 LC/MSD trap system VL. Melting points were uncorrected. TLC was performed on Merck silica gel plates with F-254 indicator; visualization was accomplished by UV light (254 nm) or by exposing to I₂ vapour. All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware using syringe-septum cap technique.

General procedure for the preparation of 2-isopropyl-2-oxazolines **2, (+)-**9** and (+)/(-)-**11**.** A solution of the proper 2-ethyl-2-oxazoline (10 mmol in 5 mL of dry THF) was added dropwise under N₂ to a precooled (–78 °C) solution of LDA (10 mmol in 5 mL of dry THF) and the resulting mixture was stirred at this temperature for 30 min before adding MeI (12 mmol). The reaction mixture was then warmed up to room temperature, quenched with sat. aq. NH₄Cl, poured into 20 mL of saturated brine, extracted with Et₂O (3 × 10 mL), dried (Na₂SO₄) and the solvent evaporated under reduced pressure. Kugelrohr distillation gave the following 2-isopropyl-2-oxazolines:

4,4-Dimethyl-2-isopropyl-4,5-dihydrooxazole (2): oil, 64 %.⁵

(4R)-4-Benzyl-2-isopropyl-4,5-dihydrooxazole [(+)-9**]:** oil 75 %, [α]_D +33.8 (c 1, CHCl₃), lit. +34.2 (c 1.43, CHCl₃).⁶

(4R)-2,4-Diisopropyl-4,5-dihydrooxazole [(+)-11**]:** oil, 90 %, [α]_D +72.5 (c 1, CHCl₃).

(4S)-2,4-Diisopropyl-4,5-dihydrooxazole [(–)-11**]:** oil, 90 %, [α]_D –72.5 (c 1, CHCl₃), lit. –74.8 (c 9.43 CHCl₃).⁷

General procedure for the reaction of lithiated 2-isopropyl-2-oxazolines with nitrones. A solution of the proper 2-isopropyl-2-oxazoline (1 mmol) and TMEDA (1.5 mmol) in THF (10 mL) at –78 °C and under N₂ was reacted with *s*-BuLi (1.5 mmol). The resulting mixture was stirred for 1 h at this temperature before adding a solution of nitrone **4** (0.9 mmol in 2 mL of THF). Then, the reaction mixture was warmed up to room temperature, quenched with sat. aq. NH₄Cl, poured into 20 mL of saturated brine, extracted with Et₂O (3 × 10 mL), dried (Na₂SO₄) and the solvent evaporated under

¹ Kamata, K.; Agata, I.; Meyers, A. I. *J. Org. Chem.* **1998**, 63, 3113–3116.

² a) Murahashi, S. I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.*, 55, **1990**, 1736–1744. b) Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T. *Synth. Comm.*, 24, **1994**, 2537–2550.

³ Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R. *Eur. J. Org. Chem.* **2002**, 2961–2969.

⁴ Suffert, J. *J. Org. Chem.* **1989**, 509–510.

⁵ Meyers, A. I.; Smith, E. M.; Ao, M. S. *J. Org. Chem.* **1973**, 38, 2129.

⁶ Bates, G. S.; Varelas, M. A. *Can. J. Chem.* **1980**, 2562.

⁷ Kurth, M. J.; Decker, O. H W.; Hope, H.; Yanuck, M. D. *J. Am. Chem. Soc.*, 107, **1985**, 443–448.

reduced pressure. The crude mixture was flash-chromatographed (silica gel; petroleum ether: AcOEt = 8-9:2-1) to give spirocyclic compounds **5a–e** with the following data:

2-tert-Butyl-4,4,8,8-tetramethyl-3-phenyl-1,6-dioxo-2,9-diazaspiro[4.4]nonane (5a). White solid, mp 67–69 °C (hexane), 70 %. Spectroscopic data have been reported in ref. 3.

2-tert-Butyl-4,4,8,8-tetramethyl-3-*p*-chlorophenyl-1,6-dioxo-2,9-diazaspiro[4.4]nonane (5b). White solid, mp 105–108 °C (hexane), 74 %. ¹H NMR (500 MHz, CDCl₃) δ: 0.75 (s, 3 H), 0.83 (s, 3 H), 0.95 (s, 9 H), 1.14 (s, 3 H), 1.32 (s, 3 H), 2.00–2.50 (br. s, exchanges with D₂O, 1 H), 3.60 (d, *J* = 7.5, 1 H), 3.70 (d, *J* = 7.5, 1 H), 4.20 (s, 1 H), 6.90–7.00 (m, 1 H), 7.20–7.40 (m, 2 H), 7.60–7.70 (m, 1 H). ¹³C NMR (75 MHz, CDCl₃) δ: 19.1, 19.8, 26.8, 27.3, 28.8, 48.8, 55.9, 59.4, 70.2, 76.9, 121.8 (spiro carbon), 127.6, 128.5, 130.5, 132.5, 139.1. MS (ESI) *m/z* (%): 375 [M+Na]⁺ (100), 353 [M+H]⁺ (27). FT-IR (KBr) cm⁻¹: 3386, 2970, 1473, 1381, 1088, 1110, 966. Anal. Calcd. for C₁₉H₂₉ClN₂O₂: C, 64.67; H, 8.28; N, 7.94. Found: C, 64.55; H, 8.33; N, 7.95.

2-tert-Butyl-4,4,8,8-tetramethyl-3-*p*-methoxyphenyl-1,6-dioxo-2,9-diazaspiro[4.4]nonane (5c). Waxy solid, 72 %. ¹H NMR (500 MHz, CDCl₃) δ: 0.77 (s, 3 H), 0.82 (s, 3 H), 0.95 (s, 9 H), 1.14 (s, 3 H), 1.31 (s, 3 H), 2.00–2.50 (br. s, exchanges with D₂O, 1 H), 3.60 (d, *J* = 7.7 Hz, 1 H), 3.74 (d, *J* = 7.7 Hz, 1 H), 3.75 (s, 3 H), 4.16 (s, 1 H), 6.70–6.85 (m, 2 H), 6.90–7.00 (m, 1 H), 7.60–7.70 (m, 1 H). ¹³C NMR (75 MHz, CDCl₃) δ: 19.1, 19.8, 26.8, 27.3, 28.8, 48.7, 55.0, 55.8, 59.3, 70.3, 76.8, 112.5, 112.9, 121.8 (spiro carbon), 128.4, 130.1, 132.4, 158.5. MS (ESI) *m/z* (%): 371 [M + Na]⁺ (100), 349 [M + H]⁺ (48). FT-IR (KBr) cm⁻¹: 3384, 2961, 1510, 1249, 1038, 846. Anal. Calcd. for C₂₀H₃₂ClN₂O₃: C, 68.93; H, 9.26; N, 8.04. Found: C, 69.05; H, 9.44; N, 7.97.

Spirocyclic compound **5d-A** equilibrates with the corresponding hydroxylamino form **5d-B** in CDCl_3 solution. Oil, 38%. ^1H NMR (500 MHz, CDCl_3) δ : 1.06 (s, 3 H) 1.12 (s, 9 H), 1.15 (s, 9 H), 1.19 (s, 3 H), 1.23 (s, 3 H), 1.27 (s, 3 H), 1.60–1.80 (m, 7 H), 1.90–1.95 (m, 1 H), 2.86 (d, $J = 5.5$ Hz, 1 H), 3.08 (d, $J = 5.5$ Hz, 1 H), 3.20 (s, 1 H), 3.53 (d, $J = 7.9$ Hz, 1 H), 3.67 (d, $J = 7.9$ Hz, 1 H). ^{13}C NMR (75 MHz, CDCl_3) δ : 20.2, 21.02, 22.5, 22.9, 24.9, 26.4, 26.5, 26.6, 26.7, 26.8, 26.9, 27.2, 27.3, 27.5, 27.7, 28.7, 29.6, 29.8, 29.9, 41.0, 41.1, 47.6, 49.2, 55.2, 55.3, 58.5, 59.9, 69.4, 69.9, 72.4, 76.5, 120.6 (spiro carbon), 165.9 (C=N).

Spirocyclic compound **5e-A** equilibrates with the corresponding hydroxylamino form **5e-B** in CDCl₃ solution. Oil, 35 %. ¹H NMR (500 MHz, CDCl₃) δ 0.7–1.5 (38 H, *t*Bu **A** + *t*Bu **B**, 4 × CH₃ **A** + 4 × CH₃ **B**, CH₃-(CH₂)₅- **A** + CH₃-(CH₂)₅- **B**) 2.10–2.50 (br. s, exchanges with D₂O, 1 H), 2.63–2.65 (m, 1 H), 2.89–2.95 (m, 1 H), 2.96–3.00 (m, 1 H), 3.07–3.10 (m, 1 H), 3.10 (s, 1 H), 3.56–3.62 (m, 1 H), 3.65–3.70 (m, 1 H), 3.82–3.86 (m, 1 H). ¹³C NMR (75 MHz, CDCl₃) selected data δ: 12.3, 16.2, 17.5, 19.1, 20.8, 24.3, 25.2, 27.4, 28.4, 29.3, 30.1, 32.9, 44.5, 45.8, 55.8, 57.3, 58.5, 64.7, 71.0, 75.0, 119.8 (spiro carbon), 163.3 (C=N). MS (ESI) *m/z* (%) 341 [M + H]⁺ (100). FT-IR (KBr) (**A**) cm⁻¹: 3376, 2962, 1656 (C=N), 1465, 1362.

After column chromatography, the hydroxylamino derivative **10-A** was isolated. It rapidly equilibrates with the corresponding spirocyclic form **10-B** in CDCl_3 solution. White solid, 71 %, mp 86-88 °C (hexane). ^1H NMR (500 MHz, CDCl_3) δ 0.78–1.15 (6 $\times$ s, *t*Bu **A** + *t*Bu **B**, 2 $\times$ CH_3 **A** + 2 $\times$ CH_3 **B**), 2.00–2.40 (br. s, 1 H **A** + 1 H **B**, exchanges with D_2O), 2.70–3.00 (m, 2 H **A** + 2 H **B**), 3.50–3.60 (m, 2 H **A** + 2 H **B**), 3.88 (s, 1 H **A**), 3.90–4.00 (m, 1 H **A** + 1 H **B**), 4.22 (s, 1 H **B**), 7.00–7.50 (m, 10 H **A** + 10 H **B**). ^{13}C NMR (125 MHz, CDCl_3) δ : 23.5, 23.6, 25.9, 26.9, 38.8, 41.8, 47.8, 57.1, 59.1, 60.6, 65.4, 70.6, 70.9, 72.9, 118.3 (spiro carbon, **B**), 126.0, 127.4, 127.7, 128.0, 128.1, 129.0, 129.4, 137.7, 139.4, 166.6 (C=N, **A**). MS (ESI) m/z (%) 403 [$\text{M} + \text{Na}$] $^+$ (100), 381 [$\text{M} + \text{H}$] $^+$ (16). FT-IR (KBr) (**A**) cm^{-1} : 3373, 2976, 1690 (C=N), 1160, 704.

Spirocyclic compound **12a-A** rapidly equilibrates with the corresponding hydroxylamino form **13a-B** in CDCl₃ solution;⁸ as a pure spirocyclic form was obtained after crystallization.

White solid, 71 %, mp 102–105 °C (hexane). ¹H NMR (500 MHz, CDCl₃) δ: 0.80–1.05 (21 H, *t*Bu **A** + *t*Bu **B**, 2 × CH₃, **A** + 2 × CH₃, **B**, 2 × d, CH₃, **A** + 2 × d, CH₃, **B**), 1.58–1.70 (m, 1 H **A**), 1.75–1.86 (m, 1 H, **B**), 1.90–2.10 (br. s, exchanges with D₂O 1 H, **A** + **B**), 2.88–2.98 (m, 1 H, **A**), 3.40–3.48 (m, 1 H, **B**), 3.50–3.65 (m, 2 H, **B**), 2.68 (t, *J* = 7.9 Hz, 1 H, **A**), 3.98 (dd, *J* = 7.9, 6.7 Hz 1 H, **A**), 4.20 (s, 1 H, **B**), 4.22 (s, 1 H, **A**), 7.00–7.10 (m, 1 H, **A** + **B**), 7.20–7.40 (m, 3 H, **A** + **B**), 7.60–7.75 (m, 1 H, **A** + **B**). ¹³C NMR (125 MHz, CDCl₃) δ: 19.4, 19.6, 19.8, 19.9, 20.2, 23.9, 26.4, 27.1, 33.0, 48.0, 49.0, 59.7, 60.9, 62.7, 63.4, 64.8, 69.2, 70.7, 72.6, 121.4 (spiro carbon, **A**), 127.9, 128.8, 130.6, 130.8, 132.8, 136.8, 139.3, 165.9 (C=N, **B**). MS-(ESI) *m/z* (%) 355 [M + Na]⁺ (100), 333 [M + H]⁺ (6). FT-IR (KBr) (**A**) cm⁻¹: 3370, 2970, 1452, 1362, 962, 712.

⁸ Comparable results were obtained when C₆D₆ or (CD₃)₂SO were used as the solvents instead of CDCl₃.

Spirocyclic compound **12b-A** rapidly equilibrates with the corresponding hydroxylamino form **13b-B** in CDCl₃ solution; as a pure spirocyclic form was obtained after crystallization. Waxy solid, 62 % overall yield. ¹H NMR (500 MHz, CDCl₃) δ: 0.80–1.05 (21 H, *t*Bu, **A** + *t*Bu, **B**, 2 × CH₃, **A** + 2 × CH₃, **B**, 2 × d, CH₃, **A** + 2 × d, CH₃, **B**), 1.58–1.70 (m, 1 H, **A**), 1.75–1.86 (m, 1 H, **B**), 1.90–2.10 (br. s, exchanges with D₂O 1 H, **A** + **B**), 2.88–2.98 (m, 1 H, **A**), 3.40–3.48 (m, 1 H, **B**), 3.50–3.65 (m, 2 H, **B**), 2.68 (t, *J* = 7.9 Hz, 1 H, **A**), 3.98 (dd, *J* = 7.9, 6.7 Hz, 1 H, **A**), 4.20 (s, 1 H, **B**), 4.22 (s, 1 H, **A**), 7.00–7.10 (m, 1 H, **A** + **B**), 7.20–7.40 (m, 2 H, **A** + **B**), 7.60–7.75 (m, 1 H, **A** + **B**). ¹³C NMR (125 MHz, CDCl₃) δ: 19.0, 19.3, 19.5, 19.8, 20.2, 23.6, 26.0, 26.7, 32.6, 47.6, 48.7, 59.3, 62.4, 63.0, 64.4, 68.8, 70.4, 72.3, 121.1 (spiro carbon, **A**), 127.5, 128.5, 130.3, 130.4, 132.5, 138.9, 165.5, (C=N, **B**). MS-(ESI) *m/z* (%) 389 [M + Na]⁺(100), 367 [M + H]⁺(22). FT-IR (KBr) cm⁻¹ (**A**): 3392, 2974, 1492, 1407, 1090, 853, 582.

***N*-tert-Butyl-*N*-[1-cyclohexyl-2-(4-isopropyl-4,5-dihydrooxazol-2-yl)-2-**

methylpropyl]hydroxylamine (14). Waxy solid, 40 %. ¹H NMR (500 MHz, CDCl₃) δ 0.82 (d, *J* = 6.7 Hz, 3 H), 0.87 (d, *J* = 6.7 Hz, 3H), 1.11 (s, 9 H), 1.00–1.30 (m, 6 H), 1.30 (s, 1 H), 1.31 (s, 1 H), 1.50–1.85 (m, 6 H), 2.00–2.40 (br. s, exchanges with D₂O, 1 H), 2.90 (d, *J* = 5.5 Hz, 1 H), 3.28–3.36 (m, 1 H), 3.50–3.62 (m, 2 H). ¹³C NMR (75 MHz, CDCl₃) δ: 19.6, 19.8, 25.2, 26.7, 26.8, 26.9, 27.03, 27.9, 30.0, 30.1, 31.5, 41.3, 46.9, 60.3, 63.4, 64.6, 70.9, 168.6 (C=N). MS-(ESI) *m/z* (%) : 361 [M + Na]⁺(6), 339 [M + H]⁺(100). FT-IR (KBr) cm⁻¹ 3272, 2943, 1697, (C=N), 1468, 1264, 1087, 899. Anal. Calcd. for C₂₀H₃₈N₂O₂: C, 70.96; H, 11.31; N, 8.28. Found: C, 71.33; H, 11.57; N, 8.44.

Preparation of 5-Isoxazolidinones 6a–e.

Method A: To a solution of the spirocyclic compound (**5a–e**, **12a,b**) (1 mmol) in 1,4-dioxane/water (4/1 v/v, 5 mL), trifluoroacetic acid (10–20 % mol) was added and the resulting solution stirred at room temperature overnight. Then, saturated NaHCO₃ (10 mL) was added and the resulting mixture extracted with AcOEt (3 × 10 mL). The combined organic layers were dried (Na₂SO₄) and evaporated in vacuo to give a crude product that was flash-chromatographed (silica gel, petroleum ether/AcOEt 8-9/2-1) to give 5-isoxazolidinones **6**.

Method B: To a solution of the hydroxylamino derivative (**10** or **14**) (1 mmol) in THF/H₂O (4/1 v/v, 5 mL) a solution of 2% w/w (COOH)₂ (1.5 mmol) was added and the resulting mixture stirred overnight. Then, saturated NaHCO₃ (10 mL) was added and the solution extracted with Et₂O (3 × 10 mL), dried (Na₂SO₄) and the solvent evaporated under reduced pressure. The crude mixture was flash-chromatographed (silica gel; petroleum ether/AcOEt = 8-9/2-1) to give 5-isoxazolidinones **6**.

2-tert-Butyl-4,4-dimethyl-3-phenylisoxazolidin-5-one (6a). White solid, m.p. 100–102 °C (hexane), 78 %. Spectroscopic data have been reported in ref. 3.

(+)-**6a**: white solid, m.p. 100–102 °C (hexane), 78 %; er: 97/3 [*t*_{Rminor} = 25.1 min, *t*_{Rmajor} = 25.6 min on a chiraldex astec β-cyclodextrin dimethyl (B-DM) (30 m × 0.25 mm Id × 0.25 μm film thickness) capillary column, det. FID 300 °C, column head pressure 18 psi, He flow: 1.5 mL/min, split ratio 100/1, oven temperature 130 °C]. [*α*]_D +164 (c 1, CHCl₃).

(–)-**6a**: white solid, m.p. 100–102 °C (hexane); 78 %; er: 95/5 [*t*_{Rmajor} = 25.2 min, *t*_{Rminor} = 25.6 min on a chiraldex astec β-cyclodextrin dimethyl (B-DM) (30 m × 0.25 mm Id × 0.25 μm film thickness) capillary column, det. FID 300 °C, column head pressure 18 psi, He flow: 1.5 mL/min, split ratio 100/1, oven temperature 130 °C]. [*α*]_D –161 (c 1, CHCl₃).

2-*tert*-Butyl-4,4-dimethyl-3-*p*-chlorophenylisoxazolidin-5-one (6b). White solid, > 98 %. ^1H NMR (500 MHz, CDCl_3) δ : 0.90 (s, 3 H) 1.05 (s, 9 H), 1.20 (s, 3 H), 4.40 (s, 1 H), 6.98 (dd, $J = 7.9, 1.8$ Hz, 1 H), 7.28 (dd, $J = 7.9, 2.4$ Hz, 1 H), 7.33 (dd, $J = 8.5, 2.4$ Hz, 1 H), 7.62 (dd, $J = 8.5, 2.4$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ : 21.2, 22.1, 25.9, 29.6, 46.6, 61.0, 72.2, 128.2₆, 128.3₁, 128.5, 130.2, 133.9, 135.7, 178.0. GC-MS (70 ev) m/z (%): 281 (M^+ , 5), 266 (6), 138 (28), 57 (100). FT-IR (KBr), cm^{-1} : 2981, 1790 (C=O), 1492, 1160, 896. Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{ClNO}_2$: C, 63.94; H, 7.15; N, 4.97. Found: C, 64.03; H, 7.33; N, 4.81.

(+)-**6b**: white solid, m.p. 156–157 °C (hexane), > 98%, er: 97/3 [$t_{\text{Rminor}} = 43.4$ min, $t_{\text{Rmajor}} = 44.1$ min on a chiraldex astec β -cyclodextrin dimethyl (B-DM) (30 m $\times$ 0.25 mm Id $\times$ 0.25 μm film thickness) capillary column, det. FID 300 °C, column head pressure 18 psi, He flow: 1.5 mL/min, split ratio 100/1, oven temperature 130 °C]. $[\alpha]_{\text{D}} +115$ (c 1, CHCl_3).

(-)-**6b**: white solid, m.p. 160–162 °C (hexane), > 98 %, er: 95/5 [$t_{\text{Rmajor}} = 43.4$ min, $t_{\text{Rminor}} = 44.1$ min on a chiraldex astec β -cyclodextrin dimethyl (B-DM) (30 m $\times$ 0.25 mm Id $\times$ 0.25 μm film thickness) capillary column, det. FID 300 °C, column head pressure 18 psi, He flow: 1.5 mL/min, split ratio 100/1, oven temperature 130 °C]. $[\alpha]_{\text{D}} -115$ (c 1, CHCl_3).

2-tert-Butyl-4,4-dimethyl-3-*p*-methoxyphenylisoxazolidin-5-one (6c). Waxy solid, 34 %. ¹H NMR (500 MHz, CDCl₃) δ: 0.95 (s, 3 H) 1.03 (s, 9 H), 1.15 (s, 3 H), 3.79 (s, 3 H), 4.16 (s, 1 H), 6.81 (dd, *J* = 8.5, 2.4 Hz, 1 H), 6.89 (dd, *J* = 8.5, 2.4 Hz, 1 H), 6.95 (dd, *J* = 7.9, 2.4 Hz, 1 H), 7.57 (dd, *J* = 8.5, 1.8 Hz, 1 H). ¹³C NMR (75 MHz, CDCl₃) δ: 14.0, 22.6, 26.0, 31.6, 46.6, 55.2, 60.8, 72.6, 113.3, 113.7, 128.3, 129.0, 130.0, 159.4, 178.6 (C=O). GC-MS (70 ev) *m/z* (%): 277 (*M*⁺ 28), 134 (100), 262 (29), 151 (30). FT-IR (KBr) cm⁻¹: 2979, 1759 (C=O), 1513, 1245, 1032. Anal. Calcd. for C₁₆H₂₃NO₃: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.58; H, 8.69; N, 5.21.

2-tert-Butyl-4,4-dimethyl-3-cyclohexylisoxazolidin-5-one (6d). Oil, 80 %. ¹H NMR (500 MHz, CDCl₃) δ: 1.16 (s, 9 H), 1.20–1.30 (m, 6 H), 1.32 (s, 3 H), 1.34 (s, 3 H), 1.44–1.82 (m, 5 H), 3.07 (d, *J* = 5.5 Hz, 1 H). ¹³C NMR (125 MHz, CDCl₃) δ: 22.6, 26.1, 26.4, 26.7, 26.9, 27.1, 29.9, 30.6, 41.6, 45.7, 60.6, 70.9, 181.0. GC-MS (70 ev) *m/z* (%): 253 (*M*⁺ 4), 170 (34), 114 (100), 83 (18), 57 (86). FT-IR (KBr) cm⁻¹: 2928, 1762, 1463, 1155. Anal. Calcd. for C₁₅H₂₇NO₂: C, 71.10; H, 10.74; N, 5.53. Found: C, 71.33; H, 10.92; N, 5.61.

(+)-**6d**: oil, 80 %, er: 98/2 [*t*_{Rminor} = 39.7 min, *t*_{Rmajor} = 41.4 min on a chiraldex astec β-cyclodextrin dimethyl (B-DM) (30 m × 0.25 mm Id × 0.25 μm film thickness) capillary column, det. FID 300 °C, column head pressure 18 psi, He flow: 1.5 mL/min, split ratio 100/1, oven temperature 130 °C]. [α]_D + 65.3 (c 1 CHCl₃).

2-*tert*-Butyl-4,4-dimethyl-3-heptylisoxazolidin-5-one (6e). Oil, > 98%. ^1H NMR (500 MHz, CDCl_3) δ : 0.85 (t, J = 6.7 Hz, 3 H) 1.15 (s, 9 H), 1.25 (s, 3 H), 1.26 (s, 3 H), 1.18–1.40 (m, 8 H), 1.42–1.60 (m, 2 H), 1.32–1.80 (m, 2 H), 3.10 (dd, J = 9.8, 3.0 Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ : 14.0, 20.2, 22.6, 24.6, 25.8, 26.4, 29.0, 29.8, 31.1, 31.7, 45.5, 60.6, 68.0, 179.7 (C=O). GC-MS (70 ev) m/z (%): 269 (M^+ 5), 254 (14), 114 (27), 84 (42), 57 (100), 43 (40). FT-IR (film) cm^{-1} : 2962, 1767 (C=O), 1465, 1389, 1156. Anal. Calcd. for $\text{C}_{16}\text{H}_{31}\text{NO}_2$: C, 71.33; H, 11.60; N, 5.20. Found: C, 71.57; H, 11.83; N, 5.39.

Figure S1. ORTEP view of the spirocyclic compound (*R,R,R*)-12a.

General procedure for the preparation of β -amino acids 7a-d: To a solution of the 5-isoxazolidinone **6** (0.5 mmol) in MeOH (5 mL) 10 % Pd on charcoal (10 % w/w) was added and the resulting mixture hydrogenated in a “Büchi Mini Clave” apparatus at 20 bar overnight. Then, the solution was filtered on a celite pad and the solvent evaporated in vacuo affording the β -amino acid **7** which did not need further purification.

3-*tert*-Butylamino-2,2-dimethyl-3-phenylpropanoic acid (7a). White solid, mp 221 dec. (Et_2O), > 98 %. ^1H NMR (500 MHz, CD_3OD) δ : 0.91 (s, 3 H), 1.21, (s, 9 H), 1.25 (s, 3 H), 4.43 (s, 1 H), 7.20–7.60 (m, 5 H). ^{13}C NMR (125 MHz, CD_3OD) δ : 21.0, 24.4, 27.5, 45.5, 58.7, 64.7, 129.8, 130.1, 153.7, 183.4 (C=O). MS-ESI m/z (%): 250 [$\text{M}+\text{H}$] $^+$ (100), 521 [M_2+Na] $^+$ (15); 248 [$\text{M}-\text{H}$] $^-$ (100), 519 [$(\text{M}-\text{H})_2+\text{Na}$] $^-$

(13). FT-IR (KBr) cm^{-1} : 3441, 2974, 1625, 1457, 1399, 1188. Anal. Calcd. for $\text{C}_{15}\text{H}_{23}\text{NO}_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.51; H, 9.63; N, 5.78.

(+)-**7a**: white solid, mp 221 dec. (Et_2O), > 98 %, $[\alpha]_{\text{D}} + 30$ (c 1, MeOH).

(-)-**7a**•HCl: white solid, mp 249–250 dec. (Et_2O), > 98 %, $[\alpha]_{\text{D}} -4.6$ (c 1, MeOH). ^1H NMR (500 MHz, CD_3OD) δ : (0.98 (s, 3 H), 1.21 (s, 9 H), 1.29 (s, 3 H), 4.79 (s, 1 H), 7.40–7.70 (2 m, 5 H). ^{13}C NMR (125 MHz CD_3OD) δ : 19.9, 25.5, 27.5, 46.5, 62.1, 65.0, 130.1, 130.7, 135.0, 180.0 (C=O). FT-IR (KBr) cm^{-1} : 3443, 2977, 2594 (NH_2^+), 2491 (NH_2^+), 1691, 1562, 1526, 1459, 1404, 1381, 1194, 1171.

3-tert-Butylamino-2,2-dimethyl-3-*p*-methoxyphenylpropanoic acid (7b). White solid, mp 208–209 dec. (hexane), > 98%. ^1H NMR (500 MHz, CD_3OD) δ : 0.92 (s, 3 H), 1.21 (s, 9 H), 1.24 (s, 3 H), 3.82 (s, 3 H), 4.40 (s, 1 H), 6.90–7.00 (m, 2 H), 7.35–7.50 (m, 2 H). ^{13}C NMR (125 MHz, CDCl_3) δ : 20.8, 24.5, 27.5, 45.8, 55.8, 58.8, 64.3, 107.5, 115.2, 127.4, 161.7, 183.4 (C=O). MS-ESI m/z (%): 278 $[\text{M}-\text{H}]^-$ (100), 579 $[(\text{M}-\text{H})_2+\text{Na}]^-$ (6). FT-IR (KBr) cm^{-1} : 3435, 2983, 1614, 1522, 1402, 1375, 1185, 1034, 848. Anal. Calcd. for $\text{C}_{16}\text{H}_{25}\text{NO}_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 69.07; H, 9.38; N, 5.35.

3-tert-Butylamino-3-cyclohexyl-2,2-dimethylpropanoic acid (7c). Oil, > 98 %. ^1H NMR (500 MHz, CDCl_3) δ : 1.20 (s, 3 H), 1.28 (s, 3 H), 1.31 (s, 9 H), 1.18–1.40 (m, 5 H overlapping singlets at 1.20, 1.28 and 1.31 ppm), 1.54–1.82 (m, 6 H), 2.70 (d, $J = 0.8$ Hz, 1 H). ^{13}C NMR (125 MHz, CDCl_3) δ : 17.9, 23.0, 25.9, 26.6, 28.1, 29.2, 40.6, 43.7, 54.3, 64.2, 180.1 (C=O). MS-ESI m/z (%): 256 $[\text{M}+\text{H}]^+$ (100), 533 $[\text{M}_2+\text{Na}]^+$ (9); 254 $[\text{M}-\text{H}]^-$ (100), 531 $[(\text{M}-\text{H})_2+\text{Na}]^-$ (9). FT-IR (KBr) cm^{-1} : 3406, 2929, 2652, 2471, 1709, 1615, 1448, 1404, 1199, 972. Anal. Calcd. for $\text{C}_{15}\text{H}_{29}\text{NO}_2$: C, 70.54; H, 11.45; N, 5.48. Found: C, 70.89; H, 11.72; N, 5.66.

(-)-**7c**: oil, > 98 %. $[\alpha]_{\text{D}} -11$ (c 1, CHCl_3).

3-tert-Butylamino-2,2-dimethyl-3-heptylpropanoic acid (7d). White solid, mp 150–151 (hexane), > 98%. ^1H NMR (500 MHz, CD_3OD) δ : 0.91 (br. t, 3 H), 1.17 (br. s, 5 H), 1.20–1.40 (m overlapping s at 1.38 ppm, 19 H), 1.44–1.63 (m, 2 H), 1.80–1.92 (m, 1 H), 3.03 (d, $J = 6.1$ Hz, 1 H). ^{13}C NMR (125 MHz, CD_3OD) δ : 14.5, 21.0, 23.6, 27.0, 30.0, 30.8, 31.0, 31.2, 32.9, 46.1, 58.1, 60.7, 183.3 (C=O). MS-ESI m/z (%): 270 $[\text{M}-\text{H}]^-$ (100). FT-IR (KBr) cm^{-1} : 3427, 2922, 2645, 2446, 1624, 1601, 1400, 1366, 1347. Anal. Calcd. for $\text{C}_{16}\text{H}_{33}\text{NO}_2$: C, 70.80; H, 12.25; N, 5.16. Found: C, 71.17; H, 12.44; N, 5.19.