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ORIGINAL ARTICLE

# Synthesis of 2-azaspiro[3.3]heptane-derived amino acids: ornitine and GABA analogues

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**Abstract** Synthesis of 6-amino-2-azaspiro[3.3]heptane-6-carboxylic acid and 2-azaspiro[3.3]heptane-6-carboxylic acid was performed. Both four-membered rings in the spirocyclic scaffold were constructed by subsequent ring closure of corresponding 1,3-bis-electrophiles at 1,1-*C*- or 1,1-*N*-bis-nucleophiles. The two novel amino acids were added to the family of the sterically constrained amino acids for the use in chemistry, biochemistry, and drug design.

**Keywords** Tailor-made amino acids · Spiro azetidines · Ornitine analogues · GABA analogues · Molecular rigidity

## Introduction

The amino acids which possess sterically constrained molecular framework occupy a distinctive class of organic compounds which arouse much interest of chemists and biologists in the last decade. A number of tailor-made sterically constrained or rigid amino acids were synthesized to date (for recent reviews see Cativiela and Ordóñez 2009; Trabocchi et al. 2008; Komarov et al. 2004). The main driving force of the activity in this area is the quest for new drugs. In general, due to pre-organization of functional groups, the sterically constrained compounds can in principle be much more efficient and selective ligands for various biological targets, thus displaying pronounced biological activity (Mann 2008). Recent studies showed that this view of the ligand–target interaction is too simplified (Martin 2007); nevertheless, molecular rigidity is widely regarded as one of the most important property of approved drugs (Feher and Schmidt 2003). Sterically constrained amino acids are especially popular for the design of peptidomimetic drugs. The principles of such design were formulated long ago (Shemyakin et al. 1969; Hruby et al. 1990; Cowell et al. 2004) and have been intensively used since then. As the result, a number of the approved drugs or clinical candidates contain residues of sterically constrained amino acids. It is interesting to note that many natural amino acids are sterically constrained; the Nature has been practicing the concept of rigidification of the biologically important molecules for millions of years.

Natural and synthetic rigid amino acids are either sterically congested or cyclic (polycyclic). This is illustrated in Fig. 1 by three amino acids which occur in Nature: 2-aminoisobutyric acid (**1**), 2-azetidinecarboxylic acid (**2**), and 2,4-methanoproline (**3**). Rigid spirocyclic scaffolds have great potential in providing wide variation of spatial disposition of the functional groups. However, spirocyclic aminoacids are very rare, both among natural and tailor-made amino acids. There are only a few reports in the literature on spirocyclic analogues of natural amino acids (Weatherhead et al. 2009; Radchenko et al. 2008; Pellicciari et al. 2002; de Meijere et al. 1999; Tamm et al. 1999).

In this paper, we report syntheses of compounds **4** and **5**—2-azaspiro[3.3]heptane-derived amino acids, spirocyclic rigidified analogues of two natural amino acids, ornitine and $\gamma$-aminobutyric acid. To the best of our knowledge, spirocyclic analogues of these biologically important amino acids are not described in the literature to date. The

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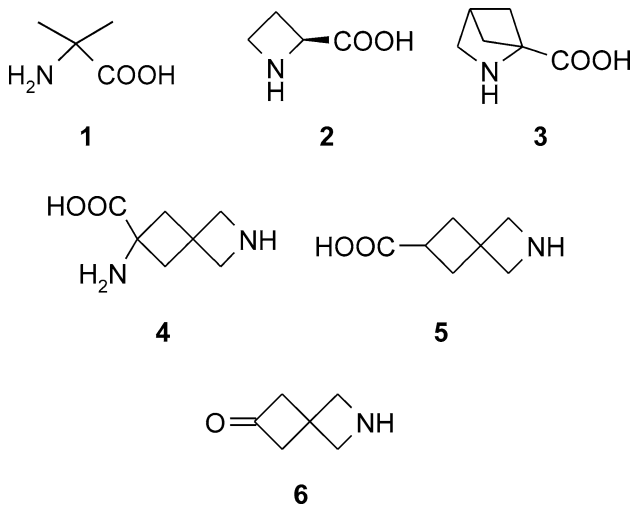



**Fig. 1** Natural sterically constrained amino acids (**1**–**3**) and compounds with 2-azaspiro[3.3]heptane scaffold (**4**–**6**)

2-azaspiro[3.3]heptane scaffold has recently captured attention of synthetic and medicinal chemists—compound **6** was suggested as an entry to structural surrogates of 4-substituted piperidines, building blocks for drug design (Meyers et al. 2009). It should also be noted that compounds **4** and **5** are non-chiral; the former being an example of a non-chiral analogue of the chiral natural amino acid, ornitine (for some other examples of non-chiral bicyclic amino acids see Avenoza et al. 2001; Rammeloo et al. 2002; Radchenko et al. 2009).

## Materials and methods

### General

Solvents were purified according to the standard procedures. (3,3-dimethoxycyclobutane-1,1-diyl)dimethanol **10** (Radchenko et al. 2008) and 2-phenyl-5,5-di(bromomethyl)-1,3-dioxane **16** (Allinger and Tushaus 1965) were prepared using the procedures reported in the literature. All other starting materials were purchased from Acros, Merck, and Fluka. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. $^{1}$H, $^{13}$C NMR, and all 2D NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 499.9 MHz for protons, 124.9 MHz for carbon-13) and Varian Unity Plus 400 spectrometer (at 400.4 MHz for protons, 100.7 MHz for carbon-13). Chemical shifts are reported in ppm downfield from TMS ($^{1}$H, $^{13}$C) as an internal standard. IR spectra were obtained on Nicolet Nexus 470 spectrometer. $\nu_{max}$ (cm$^{-1}$) values in IR spectra are given for the main absorption bands. HPLC–MS analyzes were done on an Agilent 1100 LCMSD SL instrument [chemical ionization (CI)] and Agilent 5890 Series II 5972 GCMS instrument [electron impact ionization (EI)]. Elemental analyzes were performed on Elementar Vario MICRO Cube CHNS/O analyzer.

### Methanesulfonic acid 1-methanesulfonyloxymethyl-3,3-dimethoxycyclobutylmethyl ester **11**

To a solution of **10** (4.81 g, 27.4 mmol) in chloroform (50 mL), triethylamine (11.46 mL, 82.2 mmol) was added. The resulting solution was cooled to −30°C, and mesyl chloride (5.09 mL, 65.8 mmol) was added dropwise. After the addition was complete, the reaction mixture was heated to ambient temperature, stirred for 1 h and washed with water (1 × 25 mL), 10% aqueous citric acid (1 × 25 mL) and brine (1 × 25 mL). Drying of solution with sodium sulfate and evaporation at reduced pressure led to **11** (9.10 g, 100%): mp 96°C (EtOH). MS (*m*/*z*, CI) 333 ($MH^+$). Anal. calcd for $C_{10}H_{20}O_8S_2$ C 36.14, H 6.06, S 19.29. Found C 36.19, H 6.31, S 19.04. IR (KBr, cm$^{-1}$): 1,355 ($\nu_{as}(SO_2)$), 1,174 ($\nu_s(SO_2)$). $^{1}$H NMR (DMSO-$d^6$) $\delta$ 4.20 (s, 4H, $CH_2OMs$), 3.20 (s. 6H), 3.05 (s, 6H), 2.04 (s, 4H, $C(CH_2)_2C$); $^{13}$C NMR (DMSO-$d^6$) $\delta$ 98.7 ($C(OMe)_2$), 72.0 ($CH_2OMs$), 48.4, 37.1, 36.2, 32.6.

### 6,6-Dimethoxy-2-(toluene-4-sulfonyl)-2-azaspiro[3.3]heptane **12**

A solution of **11** (9.1 g, 27.4 mmol), potassium carbonate (18.9 g, 137 mmol) and tosyl amide (4.91 g, 28.7 mmol) in DMSO (50 mL) was heated at 85°C for 30 h. After cooling, water (100 mL) was added, and the product was extracted with dichloromethane (3 × 50 mL). The combined organic phases were washed with 10% aqueous citric acid (50 mL) and brine (3 × 50 mL). Drying of the solution with sodium sulfate and evaporation in vacuo led to **12** (5.03 g, 59%) pure enough for the next step. Mp 114°C (EtOH). MS (*m*/*z*, CI) 312 ($MH^+$), 280. IR (KBr, cm$^{-1}$): 1,339 ($\nu_{as}(SO_2)$), 1,280, 1,157 ($\nu_s(SO_2)$), 1,107, 1,042. $^{1}$H NMR (DMSO-$d^6$) $\delta$ 7.67 (d, $J = 8.0$ Hz, 2H), 7.48 (d, $J = 8.0$ Hz, 2H), 3.64 (s, 4H, $C(CH_2)_2N$), 2.93 (s, 6H, $C(OCH_3)_2$), 2.42 (s, 3H, $C_6H_5CH_3$), 2.02 (s, 4H, $C(CH_2)_2C$); $^{13}$C NMR (DMSO-$d^6$) $\delta$ 144.4, 131.2, 130.4, 128.7, 99.2 ($C(OMe)_2$), 62.2, 48.6, 42.2, 28.8, 21.6.

### 2-(Toluene-4-sulfonyl)-2-azaspiro[3.3]heptan-6-one **13**

Compound **12** (3 g, 9.64 mmol) was mixed with 3 N HCl (100 mL) and stirred vigorously for 12 h. The solid formed was filtered and dried on air to yield **13** (2.41 g, 94%): mp

180–182°C (EtOH); MS (*m/z*) 266 ($MH^+$). Anal. calcd for $C_{13}H_{15}NO_3S$ C 58.85, H 5.70, N 5.28, S 12.08. Found C 58.99, H 5.45, N 5.03, S 11.87. IR (KBr, $cm^{-1}$): 1,785 ($\nu$(C=O)), 1,338 ($\nu_{as}(SO_2)$), 1,158 ($\nu_s(SO_2)$). $^1$H NMR (DMSO-$d^6$) $\delta$ 7.69 (d, $J = 7.5$ Hz, 2H), 7.49 (d, $J = 7.5$ Hz, 2H), 3.85 (s, 4H, $C(CH_2)_2N$), 3.07 (s, 4H, $C(CH_2)_2C$), 2.42 (s, 3H, $C_6H_5CH_3$); $^{13}$C NMR (DMSO-$d^6$) $\delta$ 205.8, 144.5, 131.5, 130.4, 128.7, 61.5, 57.0, 27.8, 21.6.

2-(Toluene-4-sulfonyl)-2,7,9-triaza-dispiro[3.1.4.1]undecane-8,10-dione **14**

Ketone **13** (0.8 g, 3.02 mmol), potassium cyanide (0.3 g, 4.61 mmol) and ammonium carbonate (0.87 g, 9.05 mmol) were dissolved in a mixture of EtOH (8 mL) and water (3.3 mL). The mixture was stirred at 50°C for 2 days and acidified with 1 N HCl to pH = 1. The precipitate formed was filtered and dried to yield 0.62 g (61%) of **14** as a white solid: mp 241°C (EtOH); MS (*m/z*, CI) 336 ($MH^+$), 311. Anal. calcd for $C_{15}H_{17}N_3O_4S$ C 53.72, H 5.11, N 12.53, S 9.56. Found C 53.93, H 5.11, N 12.72, S 9.69. IR (KBr, $cm^{-1}$): 1,758 and 1,710 ($\nu$(C=O)), 1,402, 1,340 ($\nu_{as}(SO_2)$), 1,161 ($\nu_s(SO_2)$). $^1$H NMR (DMSO-$d^6$) $\delta$ 10.56 (s, 1H, NH), 8.1 (s, 1H, NH), 7.69 (d, $J = 6.5$ Hz, 2H), 7.48 (d, $J = 6.5$ Hz, 2H), 3.76 (br s, 2H), 3.66 (br s, 2H), 2.41 (s, 3H), 2.24 (m, 4H); $^{13}$C NMR (DMSO-$d^6$) $\delta$ 178.6, 156.4, 144.5, 131.3, 130.4, 128.7, 63.0, 61.1, 57.6, 42.2, 30.2, 21.6.

6-amino-2-azaspiro[3.3]heptane-6-carboxylic acid **4**

Compound **14** (200 mg, 0.57 mmol) was added to solid sodium amalgam (3.9 g) in methanol (15 mL). The reaction mixture was heated at reflux for 6 h. The solution was decanted from the liquid amalgam, and the residue was washed with methanol (10 mL). The solvent was evaporated in vacuo and the residue was dissolved in DME (4 mL). $Boc_2O$ (0.68 g, 3.1 mmol), $NEt_3$ (0.25 mL, 1.79 mmol) and DMAP (2 mg, 0.016 mmol) were added in succession. Reaction mixture was stirred overnight at ambient temperature and concentrated in vacuo. The residue was taken up in $CH_2Cl_2$ (15 mL), washed with 1 N HCl (2 × 5 mL), saturated aqueous $Na_2CO_3$ (1 × 5 mL) and brine (1 × 5 mL), dried over $Na_2SO_4$, filtered and concentrated to yield **15** as a yellowish oil, 0.254 g (93%, >90% purity by $^1$H NMR), which was used in the next step without further purification.

Compound **15** (0.25 g) was dissolved in DME (5 mL), and 1 N NaOH (5 mL) was added. The mixture was stirred overnight at ambient temperature. The resulting solution was partitioned between $Et_2O$ (5 mL) and water (10 mL), the aqueous layer was washed with $Et_2O$ (1 × 5 mL), acidified with 3 N HCl to adjust pH = 1 and stirred for 2 h. Water was evaporated in vacuo, the residue was purified by ion-exchange chromatography using Amberlite IR-120(plus) ion-exchange resin (25 g) as the stationary phase and 5% aqueous ammonia as an eluent yielding the amino acid **4** (45 mg, 54% from **15**): mp > 250°C, dec. (EtOH–$H_2O$). Anal. calcd for $C_7H_{12}N_2O_2$ C 53.83, H 7.74, N 17.94. Found C 53.99, H 7.95, N 18.04 IR (KBr, $cm^{-1}$): 3,479 and 3,430 ($\nu(NH_2)$), 1,633 ($\nu_{as}(COO^-)$), 1,590 ($\delta(NH_2^+)$), 1,397 ($\nu_s(COO^-)$). $^1$H NMR ($D_2O$) $\delta$ 4.22 (s, 2H) 4.06 (s, 2H), 2.73 (d, $J = 14.5$ Hz, 2H), 2.53 (d, $J = 14.5$ Hz, 2H); $^{13}$C NMR ($D_2O$) $\delta$ 176.9, 58.3, 56.1, 53.7, 40.8, 34.3.

Diisopropyl 7-phenyl-6,8-dioxaspiro[3.5]nonane-2,2-dicarboxylate **17**

To a suspension of NaH (60% in mineral oil, 67 g, 1.67 mol) in dry DMF (700 mL), diisopropyl malonate (286 g, 1.52 mmol) was added dropwise (the temperature being maintained below 70°C) followed by 2-phenyl-5,5-di(bromomethyl)-1,3-dioxane **16** (266 g, 0.76 mol). The resulting reaction mixture was heated at 140°C for 15 h. After cooling, saturated $NH_4Cl$ solution (1.5 L) was added, and the product was extracted with hexanes (3 × 500 mL). The combined organic extracts were dried over sodium sulfate and concentrated in vacuo. A crystalline product formed was separated from a liquid residue by filtration, washed with hexane (2 × 100 mL) and dried to yield pure **17** (195 g, 72%) as a white solid: mp 90°C (Hexanes); MS (*m/z*, EI): 375 ($M^+$–H), 333, 317, 291. Anal. calcd. for $C_{12}H_{14}Br_2O_2$ C 41.17, H 4.03, Br 45.65. Found C 41.32, H 3.89, Br 45.58. IR (KBr, $cm^{-1}$): 1,740, 1,720 ($\nu$(C=O)). $^1$H NMR ($CDCl_3$) $\delta$ 7.47 (m, 2H), 7.36 (m, 3H), 5.41 (s, 1H, PhCH), 5.07 (m, $J = 6.5$ Hz, 2H, $CH(CH_3)_2$), 4.15 (d, $J = 11$ Hz, 2H), 3.75 (d, $J = 11$ Hz, 2H), 2.76 (s, 2H), 2.19 (s, 2H), 1.25 (d, 6.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 171.3, 138.1, 129.0, 128.3, 126.1, 101.4, 75.4, 69.1, 47.3, 37.5, 31.6, 31.3, 21.6.

Diisopropyl 3,3-bis(hydroxymethyl)cyclobutane-1,1-dicarboxylate **18**

To a solution of **17** (10 g, 26.6 mmol) in MeOH (100 mL), 10% Pd/C (2 g) was added, and the resulting suspension was hydrogenated at 5 atm and ambient temperature upon stirring for 48 h. Filtration of the catalyst and removal of the solvent in vacuo yielded **18** (7.4 g, 96%) as a colorless oil which was used in the next step without further purification. MS (*m/z*, CI) 289 ($MH^+$). $^1$H NMR ($CDCl_3$) $\delta$ 5.04 (m, $J = 6.0$ Hz, 2H, $CH(CH_3)_2$), 3.70 (br. s, 4H, $CH_2OH$), 2.66 (br. s, 2H, $CH_2OH$), 2.37 (s, 4H, $C(CH_2)_2C$), 1.22 (d, $J = 6.0$ Hz, 12H, $CH(CH_3)_2$); $^{13}$C NMR ($CDCl_3$) $\delta$ 171.6 (COO*i*Pr), 69.2, 68.5, 47.2 ($C(COOiPr)_2$), 37.9 ($C(CH_2OH)_2$), 32.7 ($C(CH_2)_2C$), 21.5 ($CH(CH_3)_2$).

Diisopropyl 3,3-bis(((methylsulfonyl)oxy) methyl)cyclobutane-1,1-dicarboxylate **19**

To a solution of **18** (6.96 g, 24 mmol) in dichloromethane (100 mL), triethylamine (10 mL, 72 mmol) was added. The resulting mixture was cooled to −30°C, and mesyl chloride (4.49 mL, 58 mmol) was added dropwise. After the addition was complete, the reaction mixture was heated to ambient temperature and stirred for 1 h, then washed with water (1 × 50 mL), 10% aqueous citric acid (1 × 50 mL) and brine (1 × 50 mL). The organic phase was dried over sodium sulfate and evaporated at reduced pressure to give dimesylate **19** (10.7 g, 100%) as a white solid. Mp 87°C (EtOH). MS (*m*/*z*, CI) 445 ($MH^+$). Anal. calcd for $C_{16}H_{28}O_{10}S_2$ C 43.23, H 6.35, S 14.43. Found C 43.07, H 6.18, S 14.51. IR (KBr, $cm^{-1}$): 1,720 ($\nu$(C=O)), 1,365 ($\nu_{as}(SO_2)$), 1,274, 1,176 ($\nu_s(SO_2)$). $^1$H NMR ($CDCl_3$) $\delta$ 5.07 (sept, $J$ = 6.0 Hz, 2H, $CH(CH_3)_2$), 4.28 (s, 4H, $CH_2OSO_2CH_3$), 3.06 (s, 6H, $CH_2OSO_2CH_3$), 2.51 (s, 4H, $C(CH_2)_2C$), 1.25 (d, $J$ = 6.0 Hz, 12H, $CH(CH_3)_2$); $^{13}$C NMR ($CDCl_3$) $\delta$: 170.6 (COO*i*Pr), 70.5, 69.7, 37.4, 35.7, 32.2, 21.5 ($CH(CH_3)_2$).

Diisopropyl 2-((4-methylphenyl)sulfonyl)-2-azaspiro[3.3]heptane-6,6-dicarboxylate **20**

A solution of **19** (9.17 g, 20.6 mmol), potassium carbonate (14.2 g, 103 mmol), and tosylamide (3.7 g, 21.7 mmol) in DMSO (50 mL) was heated at 85°C for 12 h. After cooling, water (100 mL) was added, and the product was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with 10% aqueous citric acid (50 mL) and brine (3 × 50 mL), dried over sodium sulfate and evaporated in vacuo to yield **20** (8.3 g, 81%) pure enough for the next step: mp 70°C (EtOH); MS (*m*/*z*, CI): 424 ($MH^+$), 382, 340. IR (KBr, $cm^{-1}$): 1,744, 1,722 ($\nu$(C=O)), 1,341 ($\nu_{as}(SO_2)$), 1,279, 1,159 ($\nu_s(SO_2)$), 1,102, 1,080. $^1$H NMR ($CDCl_3$) $\delta$ 7.70 (d, $J$ = 7.5 Hz, 2H), 7.35 (d, $J$ = 7.5 Hz, 2H), 4.99 (sept, $J$ = 6.0 Hz, 2H, $CH(CH_3)_2$), 3.74 (s, 4H, $C(CH_2)_2N$), 2.61 (s, 2H, $CH_2$), 2.49 (s, 3H, $C_6H_4CH_3$), 2.45 (s, 2H, $CH_2$), 1.19 (d, J = 6 Hz, 12H, $CH(CH_3)_2$); $^{13}$C NMR ($CDCl_3$) $\delta$ 170.6, 144.1, 131.6, 129.7, 128.4, 69.2, 62.1, 48.3, 41.0, 39.0, 32.5, 21.6, 21.5.

2-((4-methylphenyl)sulfonyl)-2-azaspiro[3.3]heptane-6,6-dicarboxylic acid **21**

To a solution of **20** (0.824 g, 1.95 mmol) in ethanol (5 mL), a solution of sodium hydroxide (0.26 g, 6.5 mmol) in ethanol (5 mL) was added. The resulting mixture was refluxed for 2 h, then cooled, filtered and washed with ethanol (2 × 2 mL) to give dipotassium salt of **21**. It was dissolved in water (5 mL), and the solution was acidified with 2 N HCl to pH = 2. Extraction of the resulting mixture with diethyl ether (3 × 5 mL), drying of the combined organic extracts over magnesium sulfate and evaporation of the solvent afforded dicarboxylic acid **21** (0.614 g, 93%) as a white solid: mp 231°C (EtOH); MS (*m*/*z*): 340 ($MH^+$). Anal. calcd for $C_{15}H_{17}NO_6S$ C 53.09, H 5.05, N 4.13, S 9.45. Found C 52.97, H 5.12, N 4.01, S 9.77. IR (KBr, $cm^{-1}$): 2,860–3,500 ($\nu$(O–H)), 1,708 ($\nu$(C=O)), 1,338 ($\nu_{as}(SO_2)$), 1,160 ($\nu_s(SO_2)$). $^1$H NMR (DMSO-$d^6$) $\delta$ 12.77 (br s, 2H, COOH), 7.68 (d, $J$ = 7.5 Hz, 2H), 7.48 (d, $J$ = 7.5 Hz, 2H), 3.65 (s, 4H, $C(CH_2)_2N$), 2.42 (s, 3H, $C_6H_4CH_3$), 2.31 (s, 4H, $C(CH_2)_2C$); $^{13}$C NMR (DMSO-$d^6$) $\delta$ 172.9, 144.4, 131.6, 130.3, 128.6, 62.5, 48.0, 38.9, 32.5, 21.54.

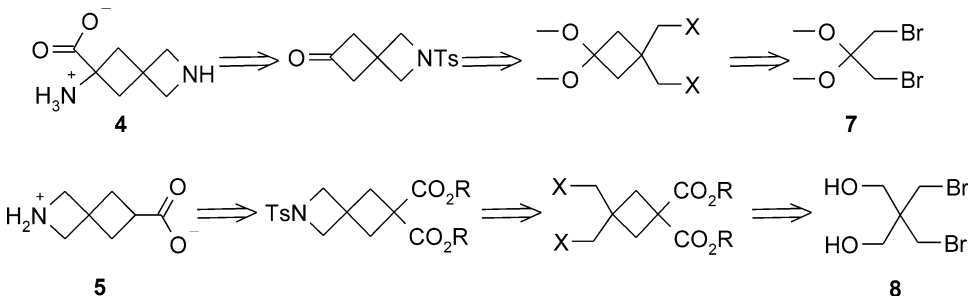
2-[(4-methylphenyl)sulfonyl]-2-azaspiro[3.3]heptane-6-carboxylic acid **22**

Dicarboxylic acid **21** (1.58 g, 4.66 mmol) was dissolved in pyridine (20 mL) and heated at reflux for 8 h. Then most of the solvent was evaporated in vacuo, 2 N HCl was added to adjust pH = 1, and the product was extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over magnesium sulfate and evaporated in vacuo to give **22** (1.29 g, 94%) as a white solid: mp 136°C (EtOH); MS (*m*/*z*, CI) 296 ($MH^+$). Anal. calcd for $C_{14}H_{17}NO_4S$ C 56.93, H 5.80, N 4.74, S 10.86. Found $C_{14}H_{17}NO_4S$ C 56.76, H 5.83, N 4.59, S 11.00. IR (KBr, $cm^{-1}$): 2,560–3,070 ($\nu$(O–H)), 1,705 ($\nu$(C=O)), 1,343 ($\nu_{as}(SO_2)$), 1,158 ($\nu_s(SO_2)$). $^1$H NMR (DMSO-$d^6$) $\delta$ 12.10 (br s, 1H, COOH), 7.67 (d, $J$ = 8.0 Hz, 2H), 7.47 (d, $J$ = 8.0 Hz, 2H), 3.67 (s, 2H, $C(CH_2)(CH_2)N$), 3.59 (s, 2H, $C(CH_2)(CH_2)N$), 2.78 (m, 1H, CHCOOH), 2.42 (s, 3H, $C_6H_4CH_3$), 2.05 (m, 4H, $CH(CH_2)_2C$); $^{13}$C NMR (DMSO-$d^6$) $\delta$ 176.1, 144.4, 131.4, 130.3, 128.7, 62.7, 62.2, 35.2, 34.3, 32.4, 21.6.

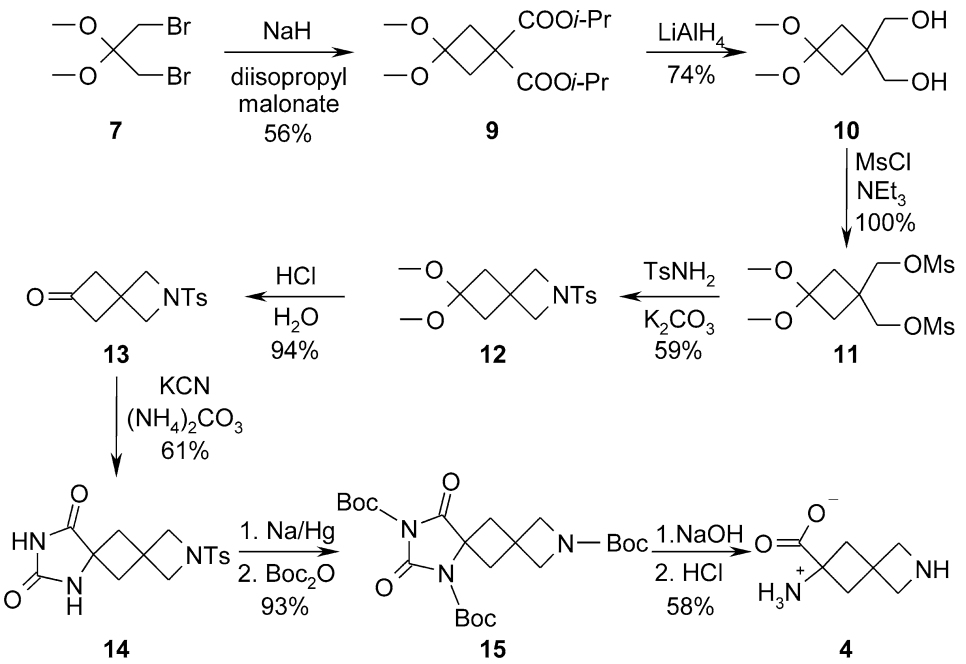
2-azaspiro[3.3]heptane-6-carboxylic acid **5**

Carboxylic acid **22** (1.29 g, 4.37 mmol) was dissolved in methanol (100 mL), and solid sodium amalgam (15 g) was added to the solution in one portion. The reaction mixture was refluxed for 8 h and then cooled. The solution was decanted from the liquid amalgam, and the residue was washed with methanol (30 mL). The solvent was evaporated in vacuo, the residue was dissolved in water, and 3 N HCl was added to adjust pH = 1. The resulting aqueous solution was washed with diethyl ether and evaporated. Purification of the residue by ion-exchange chromatography (Amberlite IR-120(plus) ion-exchange resin (50 g), 5% aqueous ammonia as an eluent) yielded amino acid **5** (0.48 g, 77%): mp 297°C, dec. (EtOH–$H_2O$). Anal. calcd for $C_7H_{11}NO_2$ C 59.56, H 7.85, N 9.92. Found C 59.65, H 7.88, N 10.01. IR (KBr, $cm^{-1}$): 3,459 ($\nu$(N–H)), 1,621

**Scheme 1** Retrosynthetic analysis of amino acids **4** and **5**




**Scheme 2** Synthesis of amino acid **4**




($\nu_{as}(COO^-)$), 1,569 ($\delta(NH_2^+)$, 1,394 ($\nu_s(COO^-)$). $^1$H NMR ($D_2O$) $\delta$ 4.07 (s, 2H, 1-$CH_2$), 3.96 (s, 2H, 3-$CH_2$), 2.80 (quint, $J = 8.5$ Hz, 1H, CHCOO), 2.39 (t, $J = 11.0$ Hz, 2H, 5-CHH and 7-CHH), 2.26 (t, $J = 11.0$ Hz, 2H, 5-CHH and 7-CHH); $^{13}$C NMR ($D_2O$) $\delta$ 183.9 (COO), 58.0 (1-$CH_2$), 57.2 (3-$CH_2$), 36.8, 35.8, 34.6.

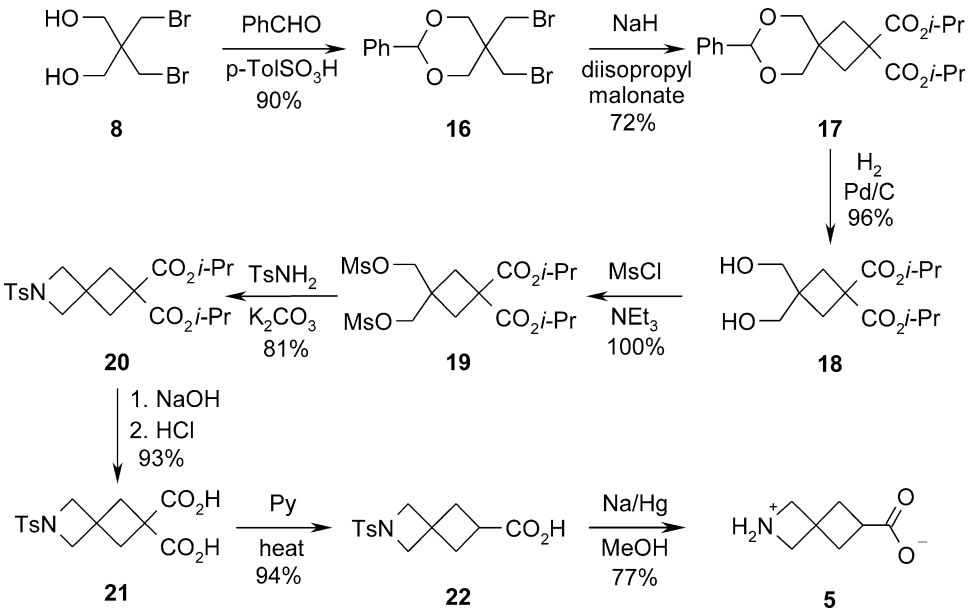
## Results and discussion

The construction of the 2-azaspiro[3.3]heptane core in both **4** and **5** was done by consequent closure of the cyclobutane and azetidine rings using bis-alkylation of malonate and tosylamide, respectively. Nevertheless, the origin of the bis-electrophile necessary for the azetidine ring construction was different. Whereas in the case of **4** the corresponding $C(CH_2X)_2$ unit originated from the malonate, in the case of **5** the fragment was already present in the starting molecule. Thus, isomeric dibromides **7** and **8** were suggested to be the appropriate starting compounds for the synthesis of **4** and **5**, respectively (Scheme 1).

The syntheses are outlined in the Schemes 2 and 3. To obtain the ornitine analogue **4**, the dibromide **7** was transformed to dimesylate **11** analogously to the method reported previously by our group (Radchenko et al. 2008). Reaction of **11** with tosyl amide under mild basic conditions resulted in the construction of 2-azaspiro[3.3]heptane ring system. Deprotection of **12** led to the formation of ketone **13**[1] which underwent Bucherer–Lieb reaction giving the dispirocyclic hydantoine **14**. Hydrolysis of **14** by heating with excess of the strong alkali was unsuccessful and led to the formation of many unidentified by-products, probably due to the azetidine ring opening. On other hand, relatively mild condition of the hydrolysis (heating to 60°C with 3.5 equivalents of 10% aqueous NaOH) resulted in no reaction. Therefore, we transformed **14** to the tris-Boc-derivative **15**; compounds of that type are known to hydrolyze under mild conditions (Wysong et al. 1996). Indeed, two-step hydrolysis of **15** afforded the amino acid **4**

[1] While the manuscript was in the preparation, an alternative synthesis of 6-oxo-2-azaspiro[3.3]heptane derivative was reported (Meyers et al. 2009).

**Scheme 3** Synthesis of amino acid **5**




which was isolated by ion-exchange chromatography (Scheme 2).

In the synthesis of the GABA analogue **5**, the dibromide **16**, which is available commercially in bulk quantities, was used to alkylate diisopropyl malonate to form the spiro-1,3-dioxane **17**. Deprotection of the diol moiety followed by bis-mesylation set up the stage for the azetidine ring formation. In the next step, 2-azaspiro[3.3]heptane ring system was constructed in a manner analogous to the transformation of **11**–**12** discussed above. Compound **20** thus obtained underwent the classic reaction sequence in malonate chemistry, hydrolysis followed by decarboxylation, leading to the formation of the carboxylic acid **22**. Pyridine was used as the solvent for the decarboxylation, as in this case the decarboxylation conditions were mild. Finally, detosylation of **22** yielded the amino acid **5** which was isolated by ion-exchange chromatography (Scheme 3).

## Conclusions

The use of 2-azaspiro[3.3]heptane scaffold in construction of functionalized sterically constrained amino acids was demonstrated for the first time. The synthesized compounds, 6-amino-2-azaspiro[3.3]heptane-6-carboxylic acid and 2-azaspiro[3.3]heptane-6-carboxylic acid are analogues of the natural compounds (ornitine and GABA, respectively) which play important roles in biological processes. Therefore, they can be advantageously used in medicinal chemistry and drug design.

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