

Synthesis of conformationally constrained, orthogonally protected 3-azabicyclo[3.2.1]octane β -amino esters

Brigitta Kazi,^a Loránd Kiss,^a Enikő Forró,^a István Mándity,^a and Ferenc Fülöp^{a,b*}

^aInstitute of Pharmaceutical Chemistry, ^bStereochemistry Research Group of the Hungarian Academy of Sciences, University of Szeged, H-6720 Szeged, Eötvös u. 6, Hungary

E-mail: fulop@pharm.u-szeged.hu

Dedicated to the memory of Professor Gábor Bernáth (1933-2009)

DOI: <http://dx.doi.org/10.3998/ark.5550190.0011.904>

Abstract

Novel azabicyclic β -amino acid derivatives were readily prepared from *diexo* or *diendo* norbornene β -amino acids. The 3-azabicyclo[3.2.1]octane skeleton was obtained by NaIO₄-mediated cleavage of the dihydroxylated β -amino ester intermediates, followed by reductive amination. Lipase-catalyzed enantioselective ring opening of racemic *exo*-norbornene β -lactam allowed preparation of the corresponding azabicyclic *exo* β -amino acid in enantiopure form.

Keywords: β -amino acids, dihydroxylation, ring opening, ring closure, enzymatic resolution

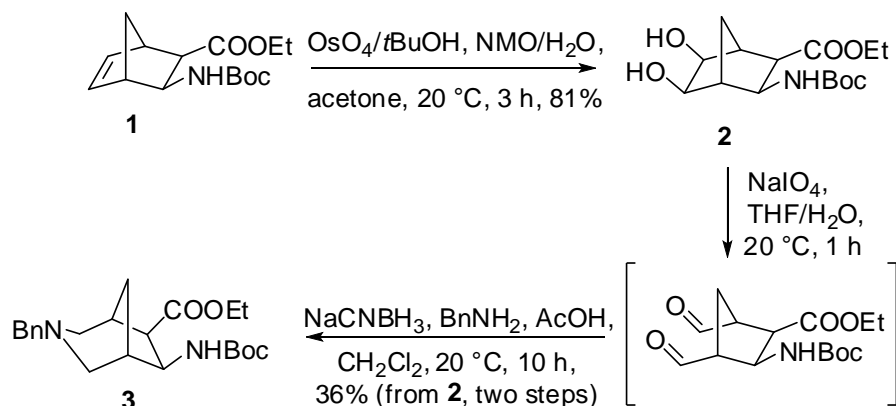
Introduction

Because of their importance in synthetic and medicinal chemistry and in peptide research, conformationally rigid, alicyclic β -amino acids have been subject to considerable interest during the past 20 years¹. *N*-Heterocyclic β -amino acids have also attracted attention in view of their biological properties and their applications in peptide synthesis.² Bicyclic α - or β -amino acids in which the *N* atom of the amino function is part of the ring system are a class of compounds of appreciable importance. Thus, bicyclic α -amino acids with the N atom in the ring system, such as 7-azabicyclo[2.2.1]heptane-1-carboxylic acid, its derivatives and compounds with an 8-azabicyclo[3.2.1]octane skeleton are conformationally restricted analogs of proline, hydroxyprolines and related proline derivatives.^{3,4} 7-Azabicyclo[2.2.1]heptane-2-carboxylic acid β -amino acids key compounds in novel β -peptide syntheses,⁵ were recently reported to behave as conformationally restricted proline analogs, acting as efficient catalysts in organocatalytic aldol processes⁶ Moreover, both bicyclic α - and β -amino acids with the *N* atom in the ring system serve as key precursors for the synthesis of medicinally valuable alkaloids such as anatoxin-*a*,⁷

epibatidine, epiboxidine etc.⁸ A number of pharmacologically active 3-azabicyclo[3.2.1]octanes have been reported as bioactive molecules,⁹ the most important of them probably being those with an amino or carboxyl function in their structure. 3-Azabicyclo[3.2.1]octane α -amino acids were recently synthesized in enantiomerically pure form,^{9a} Because of the importance of the conformationally constrained alicyclic or heterocyclic β -amino acids, our work was directed toward the synthesis of novel 3-azabicyclo[3.2.1]octane skeleton β -amino acids.

Results and Discussion

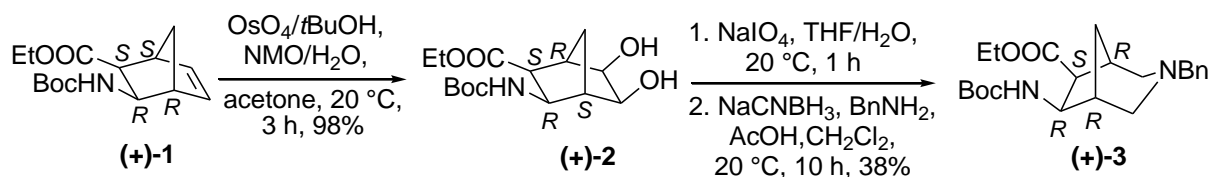
The synthetic route applied for the preparation of these azabicyclic β -amino esters is based on a simple method used for the synthesis of piperidine and azepane β -amino carboxylates.^{2a,b} The starting compounds were exo and endo norbornene β -amino acids.¹⁰ *Diexo-N*-Boc-protected norbornene amino ester **1** was transformed into the corresponding dihydroxy derivative **2** with *N*-methylmorpholine-*N*-oxide (NMO) as stoichiometric co-oxidant and OsO₄ as catalyst. A single dihydroxylated amino ester diastereomer was selectively obtained, in which the *cis* situation of the hydroxy groups relative to the methylene bridge was confirmed by NOESY experiment. NOE signals were observed between OH-5 (δ 4.63), OH-6 (δ 4.63) and H-7 (δ 1.81). Oxidative breaking of the vicinal diol C-C bond in **2** with NaIO₄ gave the corresponding dialdehyde. As this is unstable, its solution was submitted immediately, without isolation, to reductive amination with benzylamine in the presence of NaBH₃CN and AcOH. The ring-closure reaction afforded the desired azabicyclic β -amino ester **3** (Scheme 1).



Scheme 1. Syntheses of racemic azabicyclic β -amino ester **3**.

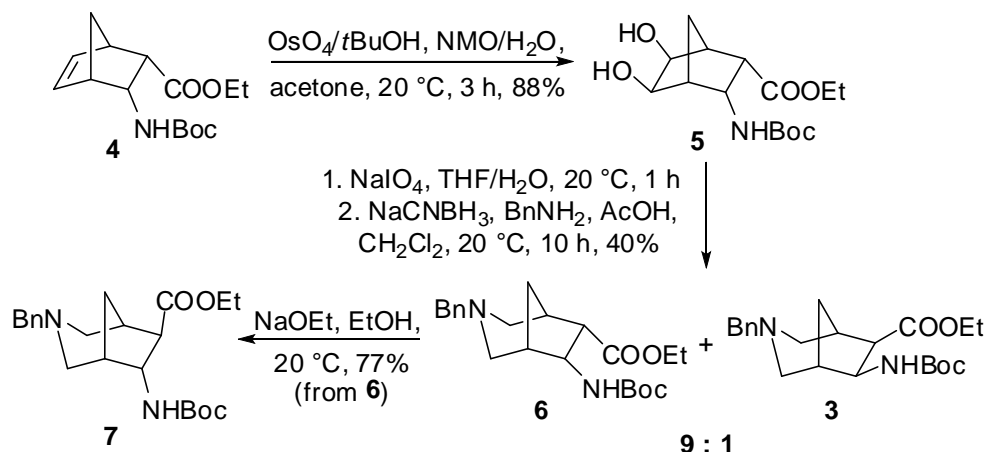
The above synthetic route was extended to the preparation of β -amino ester (+)-**3** in enantiomerically pure form (ee > 99%) from (+)-**1**, synthesized by a literature method.¹¹ Racemic norbornene β -lactam was subjected to enzymatic ring opening in the presence of CAL-B (lipase B from *Candida antarctica*, produced by the submerged fermentation of a genetically modified

Aspergillus oryzae microorganism and adsorbed on a macroporous resin) in $i\text{Pr}_2\text{O}$.¹¹ The unreacted β -lactam enantiomer was transformed into the protected amino ester (+)-**1** via lactam ring opening, followed by N-Boc protection. Further transformations (dihydroxylation, ring-cleavage and ring-closure) were performed similarly as for the racemic substances, resulting in the enantiomerically pure bicyclic β -amino ester (+)-**3** (Scheme 2).



Scheme 2. Synthesis of enantiomeric azabicyclic β -amino ester (+)-**3**.

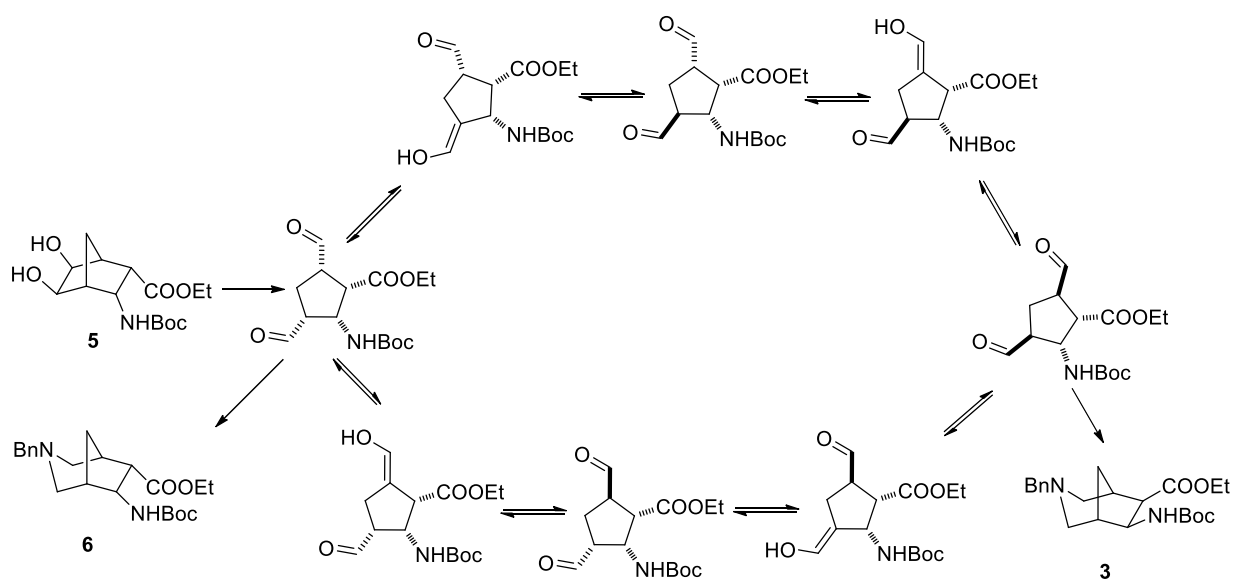
Via a synthetic procedure similar to that presented in Scheme 1, starting from *diendo* norbornene amino ester **4** through dihydroxylation, cleavage of the resulting diol and reductive amination two azabicyclic stereoisomers **6** and the earlier synthesized **3** were obtained in a ratio of 9:1 (Scheme 3). The NMR data confirmed that the major product was the desired heterocyclic *diendo* amino ester **6**, while the minor product was identified as the *diexo* compound **3** (Scheme 3).



Scheme 3. Syntheses of azabicyclic β -amino esters **3**, **6** and **7**.

The detection of **3** in this reaction mixture was somewhat surprising as it demands a simultaneous configuration change at two positions (Scheme 3). The explanation may be that the keto-enol tautomerism of the dialdehyde intermediate generated from the oxidative cleavage of diol **5**, results in the configurational change of the heterocyclic amino ester (*diendo*-*diexo*), thereby accounting for the mixture of ring closure products (Scheme 4). The heterocyclic *diendo* amino ester **6** was subjected to isomerization in the presence of NaOEt in EtOH to afford a new

azabicyclic diastereomer **7**, a C-2 epimer of **6**, in good yield (77%) with almost full conversion (Scheme 3).



Scheme 4. Possible stereoisomers of the dialdehyde intermediate due to keto-enol tautomerism.

Experimental Section

General. The chemicals were purchased from Aldrich or Fluka. The solvents were used as received from the supplier. NMR spectra were recorded on a Bruker DRX 400 spectrometer. Chemical shifts are given in δ (ppm). Optical rotations were measured with a Perkin-Elmer 341 polarimeter. Melting points were determined with a Kofler apparatus. The mass spectra were recorded on a Finnigan MAT 95S spectrometer. Elemental analyses were performed with a Perkin-Elmer CHNS-2400 Ser II Elemental Analyzer. The ee value for (+)-**3** was determined by HPLC on a Chiral Pak IA 5 μ m column (0.4 cm x 1 cm) [mobile phase: *n*-hexane/2-propanol (90/10); flow rate 0.5 mL/min; detection at 205 nm; retention time (min): 16.6 (antipode: 12.7)].

General procedure for Boc protection of amino esters

To a solution of ethyl *diexo*- or *diendo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylate hydrochloride¹⁰ (2 g, 9.23 mmol) in THF (40 mL), Et₃N (1.86 g, 18.4 mmol) and di-*tert*-butyl dicarbonate (2.21 g, 10.1 mmol) were added at 0 °C. After stirring for 20 h at room temperature, the reaction mixture was taken up in EtOAc (40 mL) and the solution was washed with H₂O (3 x 80 mL), dried over Na₂SO₄ and concentrated under reduced pressure, giving amino ester **1** or **4**.

Ethyl *diexo*-(1*S,2*S**,3*R**,4*R**)-3-(*tert*-butoxycarbonylamino)bicyclo[2.2.1]hept-5-ene-2-carboxylate (**1**).** White crystals; 96% yield; mp. 141-143 °C. ¹H NMR (DMSO, 400 MHz) δ :

1.17 (t, 3H, $J = 7.05$ Hz, CH₃), 1.37 (s, 10H, *t*Bu, H-7), 2.12 (d, 1H, H-7, $J = 9.06$ Hz), 2.45 (d, 1H, H-2, $J = 8.05$ Hz), 2.54-2.60 (m, 1H, H-1), 2.83-2.87 (m, 1H, H-4), 3.77-3.81 (m, 1H, H-3), 3.89-4.00 (m, 1H, OCH₂), 4.00-4.11 (m, 1H, OCH₂), 6.16-6.23 (m, 2H, H-5 and H-6), 6.63 (d, 1H, NH, $J = 8.81$ Hz). ¹³C NMR (DMSO, 400 MHz) δ : 14.9, 27.7, 29.1, 45.1, 45.9, 48.1, 54.0, 60.6, 78.6, 137.9, 139.7, 155.8, 173.5. Anal. Calcd for C₁₅H₂₃NO₄: C, 64.03; H, 8.24; N, 4.98. Found: C, 63.91; H, 8.20; N, 4.97.

Ethyl *diendo*-(1*R,2*S**,3*R**,4*S**)-3-(*tert*-butoxycarbonylamino)bicyclo[2.2.1]hept-5-ene-2-carboxylate (4).** White crystals; 83% yield; m.p. 86-88 °C. ¹H NMR (DMSO, 400 MHz) δ : 1.15 (t, 3H, $J = 7.08$ Hz, CH₃), 1.26-1.45 (m, 11H, *t*Bu, H-7), 2.88-2.92 (m, 1H, H-1), 2.97-3.01 (m, 1H, H-4), 3.13-3.21 (m, 1H, H-2), 3.88-4.05 (m, 2H, OCH₂), 4.38-4.49 (m, 1H, H-3), 6.62 (d, 1H, NH, $J = 8.81$ Hz), 6.15-6.21 (m, 1H, H-6), 6.28-6.34 (m, 1H, H-5). ¹³C NMR (DMSO, 400 MHz) δ : 14.9, 29.0, 46.5, 47.5, 47.8, 49.3, 54.5, 60.5, 78.8, 134.0, 138.7, 155.7, 172.7. Anal. Calcd for C₁₅H₂₃NO₄: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.00; H, 8.35; N, 5.11.

General procedure for dihydroxylation of N-Boc-protected amino esters

OsO₄ (1.43 mL, 0.08 mmol; 0.06 M solution in *t*BuOH) was added to a stirred solution of NMO (1.98 mL, 9.41 mmol; 50 wt.% in H₂O) and amino ester 1 or 4 (2.5 g, 8.88 mmol) in acetone (20 mL). After 3 h, the mixture was treated with saturated aqueous Na₂SO₃ (25 mL) and filtered through Celite, and the Celite was washed with CH₂Cl₂ (60 mL). The phases were separated and the organic layer was washed with saturated aqueous NaHCO₃ (2 × 25 mL), dried over Na₂SO₄, and concentrated under reduced pressure to give the crude solid, which was recrystallized from *n*-hexane/EtOAc. The oily compound was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 1:3).

Ethyl *diexo*-(1*R,2*S**,3*R**,4*S**)-3-(*tert*-butoxycarbonylamino)-5,6-dihydroxybicyclo[2.2.1]heptane-2-carboxylate (2).** White crystals; 81% yield; m.p. 116-118 °C. ¹H NMR (DMSO, 400 MHz) δ : 1.14 (t, 3H, $J = 7.08$ Hz, CH₃), 1.35 (s, 9H, *t*Bu), 1.61 (d, 1H, H-7, $J = 10.82$ Hz), 1.75-1.83 (m, 2H, H-7 and H-1), 2.05-2.10 (m, 1H, H-4), 2.46-3.00 (m, 1H, H-2), 3.47-3.57 (m, 2H, H-5 and H-6), 3.78-4.01 (m, 1H, H-3), 3.84-3.95 (m, 1H, OCH₂), 3.96-4.08 (m, 1H, OCH₂), 4.63 (brs, 2H, OH), 6.62 (d, 1H, NH, $J = 8.81$ Hz). ¹³C NMR (DMSO, 400 MHz) δ : 14.8, 29.0, 29.9, 46.5, 49.2, 49.7, 53.0, 60.4, 71.9, 72.6, 78.5, 155.7, 172.3. MS: (ESI, pos): $m/z = 338.2$ (M+23). Anal. Calcd for C₁₅H₂₅NO₆: C, 57.13; H, 7.99; N, 4.44. Found: C, 56.89; H, 7.80; N, 4.47.

Ethyl *diendo*-(1*S,2*S**,3*R**,4*R**)-3-(*tert*-butoxycarbonylamino)-5,6-dihydroxybicyclo[2.2.1]heptane-2-carboxylate (5).** White crystals; 88% yield; m.p. 86-88 °C. ¹H NMR (DMSO, 400 MHz) δ : 1.13-1.21 (m, 4H, CH₃ and H-7), 1.38 (s, 9H, *t*Bu), 1.75 (d, 1H, H-7, $J = 10.32$ Hz), 2.03-2.12 (m, 1H, H-4), 2.19-2.23 (m, 1H, H-1), 2.90-2.99 (m, 1H, H-2), 3.81-4.1 (m, 5H, OCH₂, H-3, H-5 and H-6), 4.45-4.63 (m, 2H, OH), 6.63 (d, 1H, NH, $J = 7.55$ Hz). ¹³C NMR (DMSO, 400 MHz) δ : 14.9, 29.0, 31.5, 44.2, 47.8, 49.0, 50.3, 60.8, 68.1, 69.5, 78.8, 156.0, 172.7. MS: (ESI, pos): $m/z = 339.1$ (M+23). Anal. Calcd for C₁₅H₂₅NO₆: C, 57.13; H, 7.99; N, 4.44. Found: C, 57.09; H, 8.12; N, 4.57.

General procedure for cleavage of dihydroxy compounds and ring closure with reductive amination

Dihydroxy compound **2** or **5** (315 mg, 1 mmol) was dissolved in THF/H₂O (11 mL, 10:1), and NaIO₄ (0.42 g, 2 mmol) was added to the solution. After stirring for 1 h at 20 °C under an Ar atmosphere, H₂O was added until the precipitation had dissolved. The mixture was extracted with CH₂Cl₂ (3 × 40 mL), the combined extract was dried over Na₂SO₄ and the resulting dialdehyde solution was immediately used for the next reaction without isolation. Benzylamine (0.11 mL, 1 mmol) and oven-dried 3 Å molecular sieve were added to the solution of the dialdehyde at 40 °C, which was next stirred for 10 min. A solution of NaCNBH₃ (63 mg, 1 mmol) and AcOH (0.057 mL, 1 mmol) in EtOH (2 mL) was added dropwise during 2 h under an Ar atmosphere. The stirring was continued for another 1 h at 40 °C. The reaction mixture was extracted in turn with 10% Na₂CO₃ (3 × 80 mL), and brine (80 mL), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, (3: R_f 0.35 *n*-hexane/EtOAc, 2:1; 6: R_f 0.35 *n*-hexane/EtOAc, 4:1).

Ethyl diexo-(1R*,5R*,6S*,7R*)-3-benzyl-7-(tert-butoxycarbonylamino)-3-azabicyclo[3.2.1]octane-6-carboxylate (3). White crystals; 36% yield (two steps); m.p. 100-103 °C. ¹H NMR (DMSO, 400 MHz) δ: 1.11-1.21 (m, 4H, CH₃ and H-8), 1.36 (s, 9H, *t*Bu), 1.95-2.02 (m, 3H, H-2, H-4, H-1), 2.08-2.22 (m, 1H, H-8), 2.30-2.35 (m, 1H, H-5), 2.52-2.61 (m, 1H, H-4), 2.62-2.76 (m, 1H, H-2), 3.03 (d, 1H, H-6, *J* = 8.31 Hz), 3.43 (s, 2H, BnCH₂), 3.80-3.95 (m, 1H, OCH₂), 3.96-4.09 (m, 1H, OCH₂), 4.22-4.26 (m, 1H, H-7), 6.76 (d, 1H, NH, *J* = 9.06 Hz), 7.20-7.38 (m, 5H, Ar-H). ¹³C NMR (DMSO, 400 MHz) δ: 14.9, 29.1, 36.0, 39.4, 42.6, 53.7, 56.7, 58.5, 59.0, 60.3, 62.3, 78.4, 127.7, 129.1, 129.4, 139.6, 155.6, 173.4. MS: (EI, pos): *m/z* = 388.5 (M). Anal. Calcd for C₂₂H₃₂N₂O₄: C, 68.01; H, 8.30; N, 7.21. Found: C, 68.17; H, 8.15; N, 7.21.

Ethyl diendo-(1S*,5S*,6S*,7R*)-3-benzyl-7-(tert-butoxycarbonylamino)-3-azabicyclo[3.2.1]octane-6-carboxylate (6). White crystals; 36% yield; m.p. 78-80 °C. ¹H NMR (DMSO, 400 MHz) δ: 1.15 (t, 3H, CH₃ *J* = 7.08 Hz), 1.37 (s, 9H, *t*Bu), 1.41-1.49 (m, 1H, H-8), 1.52-1.61 (m, 1H, H-8), 1.97 (d, 1H, H-4, *J* = 10.93 Hz), 2.06-2.14 (m, 1H, H-1), 2.19 (d, 1H, H-2, *J* = 10.52 Hz), 2.24-2.32 (m, 1H, H-5), 2.53-2.57 (m, 1H, H-4), 3.06 (dd, 1H, H-6, *J*₁ = 11.14 Hz, *J*₂ = 5.70 Hz), 3.17-3.27 (m, 2H, BnCH₂, and H-2), 3.50 (d, 1H and BnCH₂, *J* = 12.56 Hz), 4.03 (m, 2H, OCH₂), 4.15-4.27 (m, 1H, H), 6.04 (d, 1H, NH, *J* = 9.92 Hz), 7.18-7.35 (m, 5H, Ar-H). ¹³C NMR (DMSO, 400 MHz) δ: 14.9, 29.0, 35.9, 38.0, 47.2, 51.6, 54.8, 56.9, 60.2, 62.8, 78.3, 127.8, 129.1, 129.6, 139.2, 156.0, 171.9. MS: (ESI, pos): *m/z* = 389.3 (M+1). Anal. Calcd for C₂₂H₃₂N₂O₄: C, 68.01; H, 8.30; N, 7.21. Found: C, 67.88; H, 8.49; N, 7.11.

Isomerization of amino ester 6

Freshly prepared NaOEt (57 mg, 0.83 mmol) was added to a solution of **6** (250 mg, 0.64 mmol) in anhydrous EtOH (5 mL), and the mixture was stirred at room temperature for 48 h. The reaction mixture was then concentrated under reduced pressure and taken up in EtOAc (15 mL), and the organic layer was washed with H₂O (3 × 5 mL). The combined extract was dried over

Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 3:1).

Ethyl (1S*,5S*,6R*,7R*)-3-benzyl-7-(tert-butoxycarbonylamino)-3-azabicyclo[3.2.1]octane-6-carboxylate (7). Colorless oil; 77% yield. ¹H NMR (DMSO, 400 MHz) δ: 1.17 (t, 3H, CH₃, *J* = 7.08 Hz), 1.32 (s, 9H, *t*Bu), 1.36-1.39 (m, 1H, H-8), 1.62-1.72 (m, 1H, H-8), 1.96-1.99 (m, 1H, H-2), 2.07-2.27 (m, 3H, H-5, H-4 and H-1), 2.52-2.83 (m, 3H, H-2, H-4 and H-6), 3.35 (d, 1H, BnCH₂, *J* = 12.2 Hz), 3.54 (d, 1H, BnCH₂, *J* = 12.2 Hz), 3.98-4.14 (m, 3H, OCH₂ and H-7), 5.87 (d, 1H, NH, *J* = 8.08 Hz), 7.20-7.39 (m, 5H, Ar-H). ¹³C NMR (DMSO, 400 MHz) δ: 13.4, 27.7, 34.1, 37.0, 38.2, 52.3, 55.2, 58.7, 59.5, 60.9, 78.0, 126.6, 128.1, 128.8, 138.0, 154.8, 174.6. Anal. Calcd for C₂₂H₃₂N₂O₄: C, 68.01; H, 8.30; N, 7.21. Found: C, 68.02; H, 8.46; N, 7.20.

Characterization of enantiomeric compounds

All the reactions were first optimized for racemic compounds. The ¹H and ¹³C NMR spectroscopic data and elemental analyses on the enantiomeric derivatives were in accordance with those for the racemic compounds. Representative data on the enantiomers are as follows:

Ethyl (1S,2S,3R,4R)-3-(tert-butoxycarbonylamino)bicyclo[2.2.1]hept-5-ene-2-carboxylate [(+)-1]. White crystals; 99% yield; [α]_D: + 90 (*c* 0.245, EtOH); m.p. 101-103 °C.

Ethyl (1R,2S,3R,4S)-3-(tert-butoxycarbonylamino)-5,6-dihydroxybicyclo[2.2.1]heptane-2-carboxylate [(+)-2]. Yellow oil; 98% yield; [α]_D: + 41 (*c* 0.245, EtOH).

Ethyl (1R,5R,6S,7R)-3-benzyl-7-(tert-butoxycarbonylamino)-3-azabicyclo[3.2.1]octane-6-carboxylate [(+)-3]. White crystals; 38% yield; [α]_D: + 53 (*c* 0.245, EtOH); ee > 99 %; m.p. 80-82 °C.

Acknowledgements

The authors are grateful to the Hungarian Research Foundation (OTKA No F67970 and NK81371) for financial support and for the award of Bolyai János Fellowships to Loránd Kiss and Enikő Forró.

References

- (a) Kiss, L.; Forró, E.; Fülöp, F. Synthesis of carbocyclic β-amino acids. *Amino Acids, Peptides and Proteins in Organic Chemistry*. Vol. 1, Hughes, A. B., Ed. Wiley: Weinheim, 2009, 367. (b) Fülöp, F. *Chem. Rev.* **2001**, *101*, 2181. (c) Mittendorf, J.; Kunisch, F.; Matzke, M.; Militzer, H-C.; Schmidt, A.; Schönfeld, W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 433. (d) Yang, D.; Zhang, D-W.; Hao, Y.; Wu, Y-D.; Luo, S-W.; Zhu, N-Y. *Angew. Chem. Int. Ed.* **2004**, *43*, 6719. (e) Rathore, N.; Gellman, S. H.; Pablo, J. J. *Biophys. J.* **2006**, *91*, 3425. (f) Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11516. (g) Roy,

- O.; Faure, S.; Aitken, D. J. *Tetrahedron Lett.* **2006**, *47*, 5981. (h) Chandrasekhar, S.; Sudhakar, A.; Kiran, M. U.; Babu, B. N.; Jagadeesh, B. *Tetrahedron Lett.* **2008**, *49*, 7368. (i) Rua, F.; Boussert, S.; Parella, T.; Diez-Perez, I.; Branchadell, V.; Giralt, E.; Ortuno, R. M. *Org. Lett.* **2007**, *9*, 3643. (j) D'Elia, V.; Zwicknagl, H.; Reiser, O. *J. Org. Chem.* **2008**, *73*, 3262. (k) Fülöp, F.; Martinek, T. A.; Tóth, G. K. *Chem. Soc. Rev.* **2006**, *35*, 323. (l) Hetényi, A.; Mándity, I. M.; Martinek, T. A.; Tóth, G. K.; Fülöp, F. *J. Am. Chem. Soc.* **2005**, *127*, 547. (m) Torres, E.; Acosta-Silva, C.; Rua, F.; Alvarez-Larena, A.; Parella, T.; Branchadell, V.; Ortuno, R. M. *Tetrahedron* **2009**, *65*, 5669. (n) Fernandez, D.; Torres, E.; Aviles, F. X.; Ortuno, R. M.; Vendrell, J. *Bioorg. Med. Chem.* **2009**, *17*, 3824. (o) Fernandes, C.; Pereira, E.; Faure, S.; Aitken, D. J. *J. Org. Chem.* **2009**, *74*, 3217.
2. (a) Kiss, L.; Kazi, B.; Forró, E.; Fülöp, F. *Tetrahedron Lett.* **2008**, *49*, 339. (b) Kazi, B.; Kiss, L.; Forró, E.; Fülöp, F. *Tetrahedron Lett.* **2010**, *51*, 82 and references cited herein. (c) Porter, E. A.; Wang, X.; Lee, H-S.; Weisblum, B.; Gellman, S. H. *Nature* **2000**, *404*, 565. (d) Porter, E. A.; Weisblum, B.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11516. (e) Wang, G. T.; Chen, Y.; Wang, S.; Gentles, R.; Sowin, T.; Kati, W.; Muchmore, S.; Giranda, V.; Stewart, K.; Sham, H.; Kempf, D.; Laver, W. G. *J. Med. Chem.* **2001**, *44*, 1192. (f) Brown, J. R.; Nishimura, Y.; Esko, J. D. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 532. (g) Ott, G. R.; Asakawa, N.; Lu, Z.; Liu, R. Q.; Covington, M. B.; Vaddi, K.; Qian, M.; Newton, R. C.; Christ, D. D.; Traskos, J. M.; Decicco, C. P.; Duan, J. J. W. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 694.
3. (a) Avenoza, A.; Barriobero, J. I.; Busto, J. H.; Cativiela, C.; Peregrina, J. M. *Tetrahedron: Asymmetry* **2002**, *13*, 625. (b) Gil, A. M.; Bunuel, E.; Lopez, P.; Cativiela, C. *Tetrahedron: Asymmetry* **2004**, *15*, 811.
4. (a) Casabona, D.; Jimenez, A. I.; Cativiela, C. *Tetrahedron* **2007**, *63*, 5056. (b) Demizu, Y.; Shiigi, H.; Mori, H.; Matsumoto, K.; Onomura, O. *Tetrahedron: Asymmetry* **2008**, *19*, 2659.
5. (a) Otani, Y.; Futaki, S.; Kiwada, T.; Sugiura, Y.; Muranaka, A.; Kobayashi, N.; Uchiyama, M.; Yamaguchi, K.; Ohwada, T. *Tetrahedron* **2006**, *62*, 11635. (b) Pandey, G.; Laha, J. K.; Lakshmaiah, G. *Tetrahedron* **2002**, *58*, 3525.
6. Armstrong, A.; Bhonoah, Y.; White, A. J. P. *J. Org. Chem.* **2009**, *74*, 5041.
7. (a) Parsons, P. J.; Camp, N. P.; Edwards, N.; Sumoreeah, L. R. *Tetrahedron* **2000**, *56*, 309. (b) Brennehan, J. B.; Machauer, R.; Martin, S. F. *Tetrahedron* **2004**, *60*, 7301. (c) Marc, M.; Outurquin, F.; Renard, P-Y.; Créminon, C.; Franck, X. *Tetrahedron Lett.* **2009**, *50*, 4554.
8. (a) Soriano, E.; Contelles, J. M. *J. Org. Chem.* **2009**, *74*, 4061. (b) Armstrong, A.; Bhonoah, Y.; Shanahan, S. E. *J. Org. Chem.* **2007**, *72*, 8019. (c) Chen, Z. M.; Trudell, M. L. *Chem. Rev.* **1996**, *96*, 1179. (d) Aggarwal, V. K.; Olofsson, B. *Angew. Chem. Int. Ed.* **2005**, *44*, 5516. (e) Daly, J. W. *J. Med. Chem.* **2003**, *46*, 445. (f) Runyon, S. P.; Burgess, J. P.; Abraham, P.; Keverline-Franz, K. I.; Flippen-Anderson, J.; Dechamps, J.; Lewin, A. H.; Navarro, H. A.; Boja, J. W.; Kuhar, M. J.; Carroll, F. I. *Bioorg. Med. Chem.* **2005**, *13*, 2439. (g) Jin, C.; Navarro, H. A.; Carroll, F. I. *Bioorg. Med. Chem.* **2009**, *17*, 5126.
9. (a) Gelmi, M. L.; Cattaneo, C.; Pellegrino, S.; Clerici, F.; Montali, M.; Martini, C. *J. Org. Chem.* **2007**, *72*, 9811 and references cited herein. (b) Caputo, F.; Cattaneo, C.; Clerici, F.;

- Gelmi, M. L.; Pellegrino, S. *J. Org. Chem.* **2006**, *71*, 8467. (c) Brocke C.; Brimble, M. A.; Lin, D, S-H.; McLeod, M. D. *Synlett* **2004**, 2359. (d) Buckley, B. R.; Page, P. C. B.; Heaney, H.; Sampler, E. P.; Carley, S.; Brocke, C.; Brimble, M. A. *Tetrahedron* **2005**, *61*, 5876. (e) Yamashita, A.; Takahashi, N.; Mochizuki, D.; Tsujita, Yamada, S.; Kawakubo, H.; Suzuki, Y.; Watanabe, H. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2303. (f) Lew, W.; Wu, H.; Chen, X.; Graves, B. J.; Escarpe, P. A.; MacArthur, H. L.; Mendel, D. B.; Kim, C. U. *Bioorg. Med. Chem.* **2000**, *10*, 1257.
10. (a) Stájer, G.; Szabó, E. A.; Bernáth, G.; Sohár, P. *J. Chem. Soc., Perkin Trans. 1* **1987**, 237. (b) Stájer, G.; Szabó, E. A.; Bernáth, G.; Fülöp, F.; Sohár, P. *Chemische Berichte* **1987**, *120*, 259. (c) Stájer, G.; Szabó, E. A.; Fülöp, F.; Bernáth, G.; Sohár, P. *J. Heterocyclic Chem.* **1983**, *20*, 1181.
11. Forró, E.; Fülöp, F. *Tetrahedron: Asymmetry* **2004**, *15*, 573.